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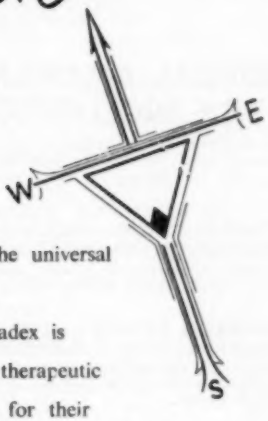

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IODINE INFORMATION

Annotated bibliographies and reviews of selected aspects of iodine usage in medicine are issued from time to time by the Chilean Iodine Educational Bureau.

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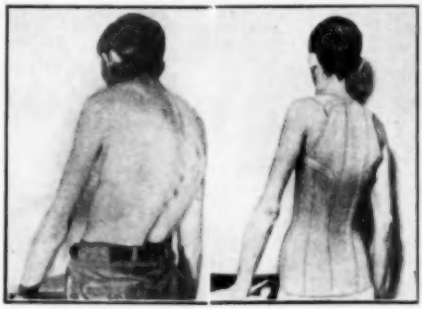
11, STONE HOUSE, BISHOPSGATE, LONDON, E.C.2.

A Spencer Spinal Support for Osteo-Arthritis



Patient with Osteo-Arthritis without—and with—a Spencer Spinal Support designed especially for him. Back brace incorporated.

Spencer Designers create supports varying from flexibility to maximum degree of rigidity. The supports may be made to whatever height in both back and front required for the individual patient. Abdominal support is co-related with back support.

In a Spencer, the patient has the precise degree of support prescribed—without the disadvantages of weight, clumsiness, and discomfort of the old-type braces.

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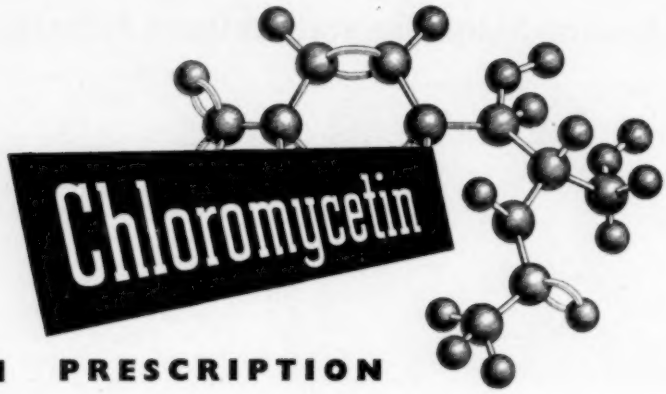

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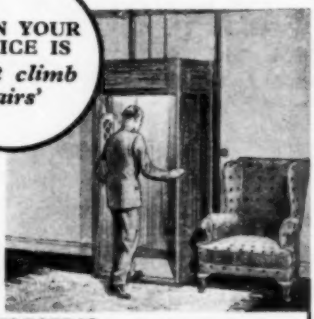

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NON-GREASY NON-ADHERENT

Reports on clinical trials indicate that remarkable results are obtained in the healing of chronic ulcers, wounds, burns and carbuncles, and that rapid control is obtained of infection due to Haemolytic Strep., Strep. Viridans, Staph Aureus, B. Pyocyaneus, B. Subtilis and B. Proteus.

Cimlac Gauze is compatible with systemic antibiotic therapy.

PACKS: Prescription: Boxes of 12 pieces 3¼" × 3¼"
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Extract of report from a London hospital, November 8, 1950:

"At this hospital, during the past year, the physician in charge of the gastro-enterological dept. has been using Bismuth Carbonate and Bourget's solution in the treatment of ulcers. The method followed is the one described by Sk. Kemp, M.D., of Copenhagen. The results have been good and patients have responded well and quickly, and this treatment is now quite an established one in the hospital."

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Period of observation	No. of patients	Symptom-free	Improved	Marked improvement	Unchanged
1— 2 yrs.	77	47 (61%)	14	(8)	14
2— 3 ,,	50	28 (56%)	15	(6)	7
3— 5 ,,	78	38 (49%)	26	(10)	12
5—10 ,,	93	37 (40%)	28	(11)	26
10—16 ,,	79	25 (32%)	34	(14)	20
TOTAL	377	175 (47%)	117	(49)	79

25-10 grm. packets of Bismuth Carbonate, free of charge, are available between January and March 1951, to members of the Medical Profession, for trial purposes.

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FOR
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Hospital trials of Tampovagan containing stilboestrol and sulphathiazole have been so successful that it has been decided to introduce a new Tampovagan pessary. Oral œstrogen therapy, formerly used in the treatment of these cases, often caused distressing side effects such as nausea, vomiting, etc., but with this modern Tampovagan therapy a quick maximal local effect is achieved without any unnecessary general effects. The dose (0.5 mgm. stilboestrol) is advocated by most authorities. Each pessary contains 0.5 mgm. stilboestrol and 0.25 gm. sulphathiazole.

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(g) Tampovagan with stilboestrol and sulphathiazole.

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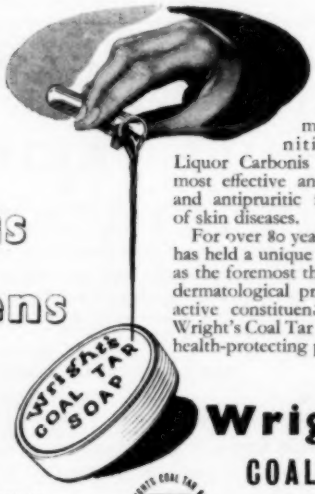
Liquor Carbonis Detergens

the principle behind Wright's Coal Tar Soap



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For over 80 years this preparation has held a unique position, not only as the foremost therapeutic agent in dermatological practice, but as the active constituent which gives to Wright's Coal Tar Soap its renowned health-protecting powers.

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IN prescribing Adrenaline Cream for the new rheumatic myalgic spot therapy, the medical profession is respectfully reminded that all tests reported in the professional press indicate that the potency of the Adrenaline in the cream used for massage is of primary importance.

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Supplies of Lloyd's product are now available through Boots, Timothy Whites and all good chemists.

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maximum therapeutic value . . .

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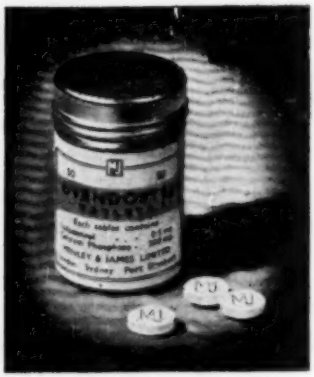

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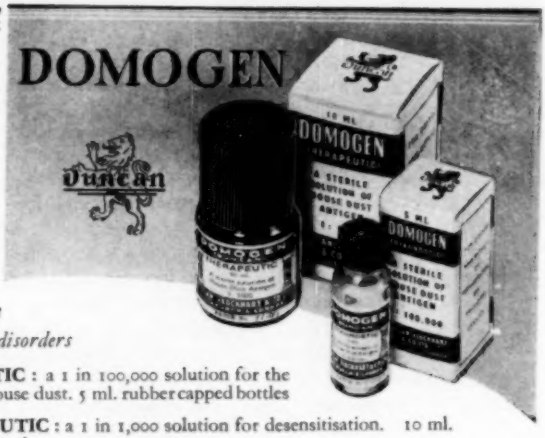

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"Celevac" tablets containers of 45, 250, and 1,000. Each tablet contains 0.5 g. methylcellulose in a palatable chocolate base.

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'ALUDROX, is available in two forms: as an amphoteric gel in 6 oz. and 12 oz. bottles and as tablets in boxes of 60.

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In conditions affecting the Pulmonary Organs

"EUPNINE VERNADE"

Eupnine Vernade is a solution containing 10 per cent. of caffeine iodide. The active substance is dissolved in a special medium, the composition of which fulfils several essential conditions. It ensures complete stability of the caffeine salt ; it increases the patient's tolerance to the drug, and it makes it more palatable.

A condition which affects the pulmonary organs cannot, in its treatment, be dissociated from consideration of cardiac strain and the possibility of renal insufficiency. An efficient therapy must be one which attempts to treat all these aspects.

INDICATIONS: Asthma, Hay-Fever, Bronchitis, Emphysema, etc., etc.

DOSAGE: Teaspoonful in a little liquid two or three times a day before meals.
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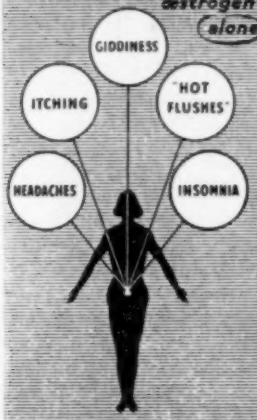

the cause: oestrogen deficiency

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tablets combine

ETHINYL ŒSTRADIOL

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SAFE SEDATIVES

Formula: † Ethinyl Œstradiol : 7.5 microgm. †† Carbromal B.P.C. : 48.75 mg. †† Bromvalerone B.P.C. : 16.25 mg.

† Ethinyl Œstradiol is "the most potent but least toxic oestrogen known . . . . "

††Carbromal and Bromvalerone are physiologically harmless open-chain ureides producing none of the habit-forming and other clinically undesirable side-effects of the barbiturates.

"MENOPAX" has no B.P., B.P.C. or N.F equivalent and may be freely prescribed as it complies with the relevant recommendations of the Cohen Report.

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whenever aspirin or salicylates are required

- EKAMMON contains Vitamin K which counteracts the prothrombin reducing action of aspirin. (*J.A.M.A.*, 1944, 125, 546).
- EKAMMON contains Vitamin C the excretion of which is accelerated by aspirin. (*Proc. Soc. Exp. Biol. Med.*, 1936, 35, 20).
- EKAMMON counteracts the Vitamin C deficiency usually present in patients suffering from rheumatoid arthritis. (*Proc. Soc. Exp. Biol. Med.*, 1936, 35, 347).
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P.2

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MILO FOOD-DRINK. Composition

Full-cream milk solids	31.8%
Malt solids	32.3%
Sugar	18.9%
Cocoa	15.5%
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The massive initial doses demanded by sulphonamide therapy have in the past involved a risk of renal blockage through crystalluria. Although modern developments have so increased the solubility of sulphonamides as to make actual blockage extremely rare, crystalluria is still commonly met with in the laboratory analysis of specimens from patients under sulphonamide treatment.

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Price to Medical Practitioners — bottles of 25 tablets, 3/7; bottles of 250 tablets, 29/3 Part I, S I, S IV, Poison, not subject to P.T.

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RIBOFLAVIN (*vitamin B_2*) 1.5 mg. per oz. NIACIN (*nicotinic acid*) 16.5 mg. per oz.
Jars: 1-oz. 8d. 2-oz. 1/1 4-oz. 2/-, 8-oz. 3/3, 16-oz. 5/9. Obtainable from Chemists and Grocer
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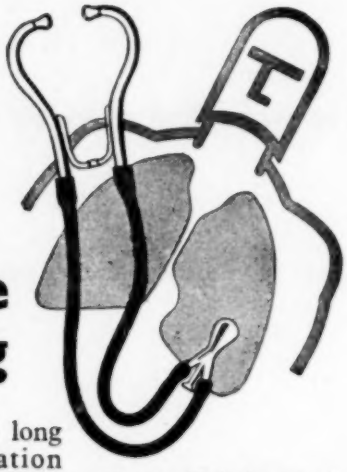

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* *Pharm. Jnl.*, 1950, 165, 126

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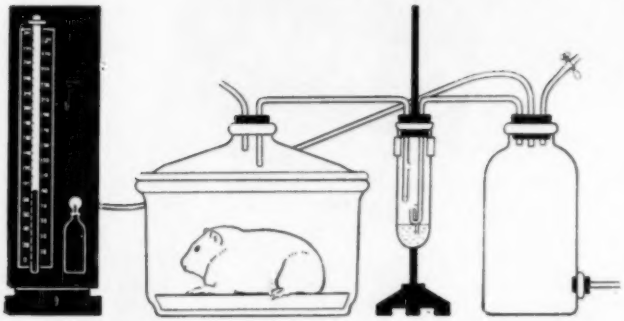

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S.93

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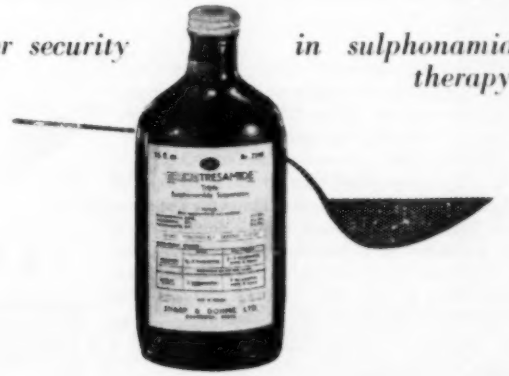

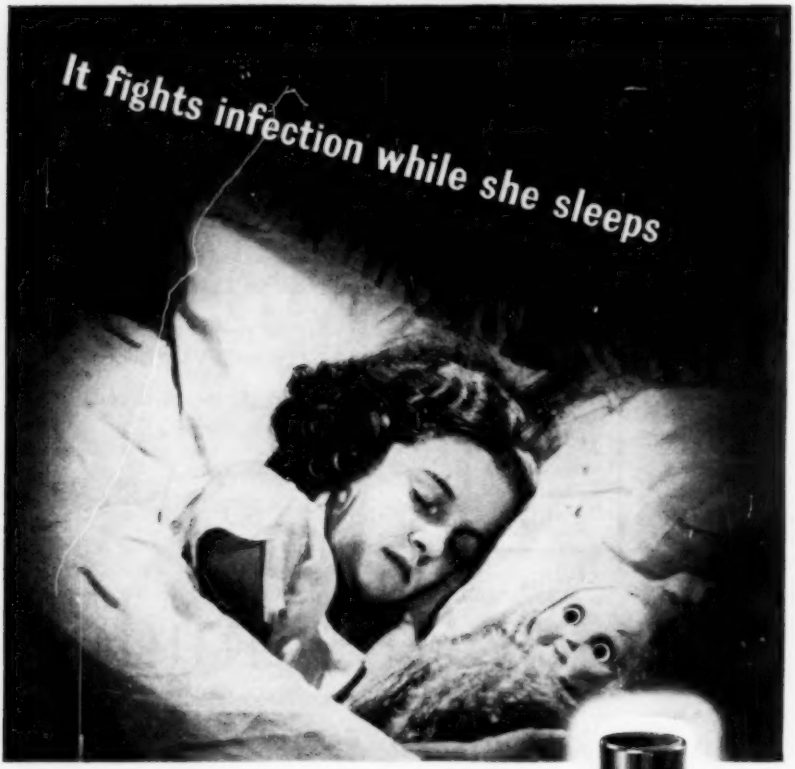

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Amidopyrine 15% Sod. 3,5-dioxo-1,2-diphenyl-4-n-butyl pyrazolidine 15% in 5 c.c. sterile solution

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SULPHADIMIDINE B.P.C. TRADE MARK

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HAMLET, ACT III, SCENE II

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Whooping Cough

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Protein	Carbohydrate	Fat	Calories
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The acceptance and rapid assimilation of glucose depends very much upon the form in which it is offered. Ordinary glucose has a sickly, even nauseating flavour but this has been entirely overcome in LUCOZADE which is a most refreshing and palatable beverage. The offer of LUCOZADE secures eager acceptance—and this ensures the full energising and therapeutic effect anticipated from glucose ingestion.

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MPI1

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' Aminacyl ' brand provides Sodium P.A.S. in dragées for convenient oral administration, thus obviating the nauseating taste of extemporized solutions and the loss of potency to be expected from stock solutions.

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Packs of 6 and 25 ampoules.

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M.357

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Vitamin Standardization
per oz.—Vitamin B_1, 0.3 m.g.;
Vitamin D, 350 i.u.; Niacin, 2 mg.

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M.356

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. . . *with related sciences to make contributions to medical progress*

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THE PRACTITIONER

No. 991 JANUARY 1951 Volume 166

THE MONTH

THOSE of us who had the privilege of visiting the Mayo Clinic in the summer of 1949 came away with two dominant impressions. One was the undoubtedly dramatic effect of compound E in rheumatoid arthritis. The other was the great care which Dr. Hench and his colleagues were taking to insist, over and over again, that their discovery was *not* the solution to the problem of rheumatism, but merely a step in this direction. The subsequent course of events has completely vindicated this point of view. The effect of cortisone, as it is now known, and of ACTH in rheumatic conditions is the greatest advance yet made in the field of rheumatic research, but it is not the final answer. Indeed, the very discovery of this effect raises so many fundamental problems that it may be some time yet before the biochemists, the endocrinologists and the pharmacologists will be in a position to provide the further data which are now required before the next advance can be made.

The Symposium

The process of consolidation has now reached such a stage that we have felt that the time has come to publish a symposium on the problem of rheumatism. This problem is ably reviewed and summed up in the introductory article by Dr. Walter Bauer of Boston, one of the ablest rheumatologists in the United States of America, and one who has had wide personal experience of the use of cortisone. Professor G. F. Marrian, as a steroid chemist of international repute, is particularly well qualified to discuss what is still a baffling problem, and the most fundamental of all, 'the hormonal disturbances of rheumatoid arthritis'. The rôle of ACTH is reviewed by Dr. F. T. G. Prunty, who has had experience of ACTH both in this country and in the United States, where he worked for a time with Professor George Thorn. The bearing of recent advances upon acute rheumatism is discussed by Dr. E. G. L. Bywaters who, as director of the research unit at the Canadian Red Cross Memorial Hospital at Taplow, has been in an advantageous position to watch and investigate such advances. No review of rheumatism today would be complete without drawing attention to two aspects of the subject which are all too liable to be overlooked in the excitement of new discoveries: the pathology of the disease, and 'the fundamental treatment of rheumatoid arthritis'. These two subjects are reviewed by two experienced workers in this field, Dr. H. J. Gibson and Dr. J. J. R. Duthie, respectively. To those harassed practitioners who are being pestered by their rheumatic patients for the 'latest' treatment, we

would particularly commend Dr. Duthie's full description of the therapeutic regime from which such patients are likely to obtain most benefit.

N.H.S. Another Year

In our review of the first year's working of the National Health Service, published in 1949, a contributor wrote, 'The National Health Service Act provides a framework round which, given vision on the part of successive ministers and an enthusiasm based on confidence on the part of doctors themselves, a service second to none can eventually be built'. There has been no succession in the post of Minister of Health; Mr. Bevan's vision seems to be limited to that of himself as Father Christmas, and the confidence of doctors in the Act and those who work it has dropped appreciably.

Three years ago we had a medical system that had grown up with the country, that had its weaknesses and its peculiarities, as is inevitable in anything that has grown naturally, but that, on the whole, gave the citizens of Britain better service than that obtainable in any other country. Today we are wallowing in the muddle of a system planned hurriedly and unskilfully, and rushed through in the face of advice. A planner in the works is worse than a spanner in the works, for a spanner is put there by someone with evil intentions and it can be removed, but planners and those who put them in the works are men of intentions so honourable that they can see nothing but base motives in those who oppose them, and they remain in the works until death or extreme senility comes to remove them. The financial experts who drafted the present scheme planned with an incompetence that would have earned them the sack in any private undertaking, but the reckless waste on inessentials which they advised or at any rate countenanced, has brought the whole service into insolvency. Yet no move is made to check the waste, but only hurried decisions to postpone promised services, and to curtail those already in existence. Not merely is the wisdom of these decisions in question, but the way in which many of them are carried out seems designed to evoke the maximum of irritation and distrust.

Registrars

The memorandum, 'Review of Appointments to Registrar Grades', issued by the Ministry of Health in November, is a tragic example of the lack of foresight which has been shown in connexion with the planning of the National Health Service. In brief, what this memorandum proposes is to reduce the number of senior registrars from 1,400 to 600, and the number of registrars from 1,400 to 1,100. The reason given for this drastic reduction is that for some years to come the number of appointments available to senior registrars who complete their training at hospitals in England and Wales is unlikely to exceed 150 annually.

The suggestion, implicit in the memorandum, that the numerical relationship between registrars and future consultant posts should be so arranged that a gradual ascent of the specialist ladder should be possible to most of those who have established themselves on its lowest rungs, is

highly dangerous. The passage from House Officer to consultant has never been a ladder in the past and it never should become one. It has been a railway with many branch lines and some sidings; the terminus may have been a consultant appointment, but branch lines, often of equal importance, led to academic posts, research posts, colonial posts, administrative or industrial posts, or to general practice with a specialist orientation. It has been a race, with prizes going to the stout of heart and strong of limb. Competition is essential to keep up the standard. The whole incident is unfortunate in the extreme. The Minister has chosen this indirect way to inform the Profession that he has abandoned the proposed expansion of consultant services which he himself had advocated a month earlier; he has issued a document having far-reaching and incalculable repercussions on specialist training and practice, apparently without consulting any individual or body familiar with hospital problems: and he has issued in November for implementation by the beginning of January, instructions which can only be reduced to sense after careful discussion.

The Merit Awards

After prolonged deliberations and inquiries, the Merit Awards Committee has issued its rewards to consultants. The names of the distinguished and the degree of their distinction have rightly been withheld. The majority of the lucky ones have kept quiet, but big Panjandra who have been given third fifteen colours and youngsters who have received unexpected additions to their income, have naturally shared their indignation and their joy with their intimate circle. Some have appealed against their grading. Wives have been indiscreet, as wives sometimes are. It is therefore possible to assess how the merit awards have been distributed, and to adumbrate to some extent the principles on which the committee has worked.

On the whole the grading has corresponded very well with the place held by the recipients in the world of their fellows. If any criticism can be made it is that the awards system has been used as an instrument of policy rather than as a recognition of merit. Nearly all clinical professors have received the highest award; it is very right that the best men should be attracted to these chairs in the future, but, owing to the method of their selection in the past, many of the present holders of these posts are second-rate.

On the equity or wisdom of the policy of merit awards there can be no agreement. There is no more equality among consultants than there is among cricketers, barristers or saxophone players, but the only grading that is of value is that which a man makes for himself by his character and the quality of his work. To be assessed and allotted to one of four pens by a group of worthies is intensely humiliating to the susceptibilities of most educated men, and it is not surprising that many of the most respected leaders in medicine and surgery have refused to allow their names to be considered and have suffered in pocket as the result. It seems inevitable that the

principle that appears to have guided the committee will become recognized in the future, that is, that the grading will be of jobs rather than men, and that the higher monetary rewards will go to those who succeed in securing posts that are recognized as conferring a leading position in the National Health service.

The Doctor in the Doldrums

WHAT is a doctor? Three years ago this question would have sounded frivolous: today it must be asked in all seriousness. Three years ago we were all doctors: it was said in the highest praise of the late Rowley Bristow that his chief merit as an orthopædic surgeon was that he was a good doctor. Today we are split into categories, each of us bearing on our rumps the rubber stamp of Ministry classification.

If by doctor, we mean a general practitioner, how is the general practitioner faring? The Collings Report served to throw a spotlight on the causes that are tending to force down the standards of men who started with the highest ideals. Under the present Act, general practice, as a cultured and humane career that should appeal to men endowed with ability, ambition and a love of their fellows, has suffered in three main ways. First, the load of routine and unintelligent work has been greatly increased and the assistance that was promised has not been forthcoming. Secondly, by exclusion from Cottage Hospitals, doctors have lost the best part of their work, the chance to care for their patients in their serious as well as their trivial ailments, and the ability to keep in touch with the advance of medicine. Thirdly, the grading of the profession into groups has placed the practitioner on a narrow road from which there is no deviation and no escape.

Sir James Cantlie Centenary

ONE of the most versatile and colourful figures in medicine and in public affairs was born a century ago, on January 17, 1851. To his contemporaries, marvelling at his genius for inventing things great and small, his untiring energy, and his restless delight in adventure, Sir James Cantlie seemed to have strayed out of a more picturesque and chivalrous era into their prosaic age.

An authority on tropical diseases, which he had studied at first hand in Egypt, India, and China, he was the moving spirit in founding the London School of Tropical Medicine, the Society of Tropical Medicine and Hygiene (as it was first called), and the *Journal of Tropical Medicine and Hygiene*. Creator of the College of Ambulance, he invented a bullet-proof ambulance stretcher for rescue work in the trenches, and a portable X-ray machine for the benefit of the poor in country places. His Volunteer Medical Staff Corps was the parent of the R.A.M.C. of the Territorial Army. Public memory associates him with the rescue of Sun Yat Sen, the 'Degeneration amongst Londoners' which caused a stir for many years, and an attack on the Eton jacket for exposing the loins. A graphic teacher, entertaining speaker and writer, and an amusing companion for young and old alike, Cantlie received a K.B.E. in 1918. He died in 1926, in his seventy-fifth year.

SPECULATIONS ON THE ETIOLOGY OF RHEUMATOID ARTHRITIS*

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RHEUMATOID arthritis is a chronic inflammatory disease, systemic in nature, characterized by the manner in which it involves joints. The absence of constant pathognomonic features makes recognition of the disease difficult when the articular manifestations are equivocal, and this explains in part why the etiological relationship of the various syndromes included under the term rheumatoid arthritis has not been established. Many of the clinical and pathological manifestations of the disease are similar to those observed in other systemic diseases of unknown etiology: specifically, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis, and scleroderma; therefore the possibility of their being related diseases has been considered. The presence of generalized anatomical alterations of the connective tissues, particularly abnormalities of the extracellular components, has led many workers to group these diseases collectively under such terms as 'collagen diseases', 'connective tissue diseases' and 'mesenchymal diseases'. These terms are not applicable to diagnosis and they do not define the morbid process of the diseases grouped together. They merely imply that anatomical studies have revealed conspicuous alterations of some constituents of connective tissue in a systemic manner.

PATHOGENESIS

Chronic inflammation is predominantly evident in rheumatoid arthritis. The extent and severity of the inflammatory process probably determines most of the clinical and laboratory manifestations of the disease. Although articular inflammation is generally the most obvious feature of rheumatoid arthritis, chronic inflammatory changes do occur in the skin, subcutaneous tissue, muscles, nerves, eyes, heart and aorta (Bauer and Clark, 1948). Careful study of other organs and tissues may reveal similar lesions.

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The inflammatory lesion of rheumatoid arthritis has no distinctive features that set it apart from other chronic inflammatory processes, except those seen in the subcutaneous nodule. Nevertheless, certain features are always present and have come to be recognized as being of diagnostic significance. These are the presence of large numbers of mononuclear cells, predominantly lymphocytes and plasma cells, particularly about small blood vessels, connective tissue proliferation and degeneration, and 'fibrinoid'. The latter is often referred to as fibrinoid degeneration, fibrinoid material, fibrinoid alteration of collagen, and fibrinoid collagen change. The term as originally applied referred to collagen fibres which assume the tinctorial and structural qualities of fibrin (Neumann, 1880). Although fibrinoid collagen change has often been considered as of basic significance in the pathogenesis of rheumatoid arthritis, too little is known concerning the composition of this material to permit of elaboration on its possible pathogenic significance. The focal collections of leucocytes are the most ubiquitous lesions, being the chief abnormality found in muscles and nerves. The proliferative phenomena are particularly prominent in articulations, and may result in pannus formation, cartilage destruction and ankylosis. This is in marked contrast to the subcutaneous nodule when connective tissue destruction is the dominant feature (Bennett, Zeller and Bauer, 1940). The centrally placed zone of necrosis, enclosed by a palisade of proliferating epithelioid cells (zone of palisading), is encircled by a heavy cellular infiltrate of lymphocytes and plasma cells. Subcutaneous nodules exhibiting these three characteristic zones present a histological pattern rarely seen in any other disease. We are hampered greatly in our interpretation of the rheumatoid process because of the paucity of early lesions for study, and the non-specificity of the histochemical methods at our disposal.

New methods are needed for better definition of structural alterations and abnormalities of ground substance in terms of physical and chemical composition and enzymatic activity. For instance, it is of interest that the chief sites of rheumatoid inflammation are tissues known to contain complex polysaccharides, such as hyaluronic acid (Meyer, 1947). The relationship of the inflammatory lesions in synovial tissues to the comparatively low concentration of hyaluronic acid with low viscosity found in rheumatoid fluids remains to be determined (Ropes *et al.*, 1947). Knowledge as to the initial alteration in tissue and the subsequent sequence of events might establish that the change in hyaluronic acid is due to a breakdown or inadequate synthesis because of the lack of a specific enzyme.

Although the clinical manifestations of rheumatoid arthritis may subside completely, the degree of reversibility of the tissue changes is not known. Observations during natural and hormone-induced remissions indicate that the inflammatory lesions are altered markedly but do not disappear completely (Giansiracusa *et al.*, 1950; Hench *et al.*, 1950). Further knowledge regarding this point may prove to be of etiological significance.

THE HYPOTHESIS OF INFECTION

Speculations on the etiology of a disease, particularly a chronic disease, are valuable because they offer an opportunity to indicate needed observations and pertinent experimentation. The sequence of events which leads to symptoms and tissue alterations is so complex that mere conjecture is generally of little value.

Parasitism or *infection* the first possibility to be considered, has during the past century explained the nature of many diseases. As a rule, the first

step in the recognition of an infectious disease has been to demonstrate its transmissibility, either by clinical or experimental study. The infectious nature of tuberculosis first became known when the disease was transmitted to animals. In the case of syphilis, its transmissibility was established by clinical observation. That failure to transmit a disease does not exclude an infectious etiology is well illustrated in the case of leprosy. In this instance the presence of Hansen's bacillus is accepted as proof that it is an infectious disease, yet experimental transmission of leprosy has never been achieved. Diseases like measles and whooping-cough are highly communicable, whereas certain fungus infections of the skin are transmitted with difficulty. These marked variations in transmissibility must always be considered when attempting to prove that a disease is infectious in nature. Another consideration of great importance is encountered even in diseases which are readily transmitted, namely, failure to reproduce many of the manifestations of the disease being investigated. Thus in experimental syphilis such features as gumma, tabes and paresis are not reproduced. Similarly, gonorrhœa is readily transmitted, yet arthritis does not occur. These two examples are not exceptions, but are characteristic of many diseases. Likewise, variations in the severity of an infectious disease may be misleading. Poliomyelitis, for example, is usually a mild disease, at times so mild as to go unrecognized; severe disease develops in only a small percentage of cases. The same is true of meningococcal infections, various types of encephalitis, tuberculosis, brucellosis, trypanosomiasis and fungus infections. Until the etiological relationship of the numerous mild cases to the infrequent severe cases is established, the transmissibility of the severe cases may not be evident from epidemiological studies.

The distribution of rheumatoid arthritis cases in no way suggests that the disease is transferred from one individual to another or that it is due to a specific environmental agent. All efforts to transmit the disease to animals have failed; nor is the disease known to occur spontaneously in the animal kingdom. If rheumatoid arthritis is a parasitic disease, susceptibility to it must be extremely variable or it must be a relatively rare manifestation of some common infectious disease. Unfortunately there are no recorded observations which warrant directing attention to the study of any of the more common infections. In rheumatic fever, provocation of the disease by upper respiratory tract infections, particularly streptococcal infections, strongly suggests that these organisms are etiologically related. Considerable evidence favouring this interpretation has been obtained from careful clinical and bacteriological studies of large groups in schools, hospitals and barracks. It is more difficult to make similar observations on patients with rheumatoid arthritis because the onset of the disease is generally insidious. Notwithstanding these difficulties, the collection of data at the time of onset of the disease may still be the most rewarding etiological approach. Any irregularities in incidence ascribable to geographical, social or occupational factors may give additional etiological information. The possible rôle of all

types of infectious agents should be considered. Failure to isolate bacteria from rheumatic fever lesions serves to emphasize the difficulties of appraising the etiological significance of infections which precede or are associated with rheumatoid arthritis. Studies pertaining to the pleuropneumonia organisms and their possible pathogenic significance in human disease are likewise of interest (Dienes *et al.*, 1948). Although found on the mucous membranes, their cultivation and transmission to animals is very difficult, despite the fact that animal strains are known to cause arthritis. That virus infections should receive consideration is suggested by recent studies which indicate that a widely distributed virus has a special affinity for muscles (Dalldorf *et al.*, 1949). The possibility of the occasional occurrence of similar but more extensive mesenchymal tissue involvement in humans with malignant infection should be investigated. Significant epidemiological observations may come to light if physicians are aware of all such possibilities. Voluntary or compulsory health insurance could enable physicians to obtain more detailed information and so facilitate greatly the collection of significant data.

Indications that a disease may be infectious in nature may come from less direct observations than those pertaining to the isolation and transmission of the infectious agent. The clinical features of a disease of unknown origin often suggest this possibility. The similarity between rheumatoid arthritis and many of the specific infectious arthritides may be so striking as to make differentiation difficult, particularly when the onset is abrupt with high fever. The many clinical similarities have long been known, and have caused earlier workers to introduce the synonym 'chronic infectious arthritis'. Laboratory tests, including synovial fluid examination, may reveal the same degree of alteration. In the case of synovial fluid this may apply both to the cytological and to the chemical changes. Histological differences are usually apparent in the synovial tissues; however, the synovitis of subacute or chronic specific infectious arthritis may offer diagnostic difficulties. The hyperglobulinæmia of rheumatoid arthritis is comparable to that found in infectious diseases, but could be due to other than an infectious agent. Such laboratory findings may well reflect chronic systemic inflammatory diseases due to other causes than infectious agents; however, the latter possibility must still be considered.

The demonstration that the sera of patients with rheumatoid arthritis of one or more years' duration often give positive agglutination tests with *beta*-hæmolytic streptococci, first reported by Dawson *et al.* (1931), has been confirmed repeatedly. Rarely do such sera exhibit the serological properties considered diagnostic for streptococcal infections, namely, significant rise in the streptolysin and fibrinolysin content. The ability of rheumatoid arthritis sera to agglutinate streptococci is not indicative of a streptococcal etiology. It probably represents a non-specific property of the sera.

For a time, *focal infections* were credited with being of etiological significance. However, the results following most thorough removals do not

support this theory. The validity of etiological theories based on the results obtained with various types of vaccine therapy have failed to be substantiated.

Failure of homologous rheumatoid nodule transplants to survive suggests that they are not due to living agents (unpublished data). Likewise, all attempts to isolate bacteria and viruses from excised nodules have been negative. The ineffectiveness of chemotherapeutic agents and antibiotics in the treatment of rheumatoid arthritis seemingly rules out any direct etiological rôle previously attached to a variety of living agents. To date, we are without evidence that rheumatoid arthritis is due to a specific infection.

ALLERGY

Since 1933, the hypothesis has frequently been made that rheumatic fever, rheumatoid arthritis and allied diseases are due to hypersensitivity (Klinge, 1933). The chief basis for this speculation is the production in animals, by antigenically active proteins, of pathological lesions which imitate in many respects those present in these diseases (Rich, 1946-47; Hawn and Janeway, 1947). Allergy develops in many infectious diseases and plays a part in the production of the pathological changes in tuberculosis, syphilis, and even in variola. Diseases in which allergy is produced by infectious agents differ from those such as hay fever, contact dermatitis and allergic reactions to drugs, in which the source of allergy is a non-living agent. Whereas infection produces a large number and variety of pathological conditions, the effects of a non-living agent are usually restricted to the body surfaces which come directly in contact with the offending agent. In food allergy the antigen is absorbed and symptoms develop in locations far removed from the original contact; however, chronic joint involvement has never been observed in such cases. Systemic symptoms due to allergy result usually from rare and unusual agents like drugs, with which the organism has no contact through phylogenetic development. Several investigators have postulated that allergy may develop to substances produced by the saprophytes of the mucous membranes, or even to the constituents of the body tissues, and be the cause of certain diseases (Cavelti, 1947). There is no human malady in which a similar mechanism is proved or made probable by the observations.

Knowledge concerning the etiology of a disease, even in infections, is not necessarily a decisive factor in understanding or controlling the disease. Observations in tuberculosis indicate that resistance and susceptibility depend in part upon the hereditary properties of the host and partly upon environmental factors. Experimental evidence of this hypothesis is being obtained. Strains of guinea-pigs and rabbits can be bred with varying resistance to tuberculosis. The difference between these strains indicates that susceptibility to tuberculosis is related to certain properties of the connective tissue (Lurie, 1941). In a disease which follows a variable course and to which susceptibility is variable, consideration of the host factors is as important as knowledge of the infectious agent. To understand the course of a disease, study of the various reactions of the organism—pathological, im-

munological and physiological—as well as the inborn or accidental factors which influence the reactions, is indispensable. Information of this type is limited. We are still unable to explain such well-known phenomena as the stages of a syphilitic infection or why malignant tuberculosis or coccidioidomycosis develops after the primary infection has healed.

That rheumatoid arthritis is an infectious disease is neither proved nor disproved. Undoubtedly many infectious agents are not yet discovered or, if known, their effects are imperfectly understood. It is likewise possible that a causative agent of rheumatoid arthritis will be discovered. Further study must include not only observations concerning the early manifestations of the disease but also the circumstances in which it occurs. All new methods which may be of aid in the recognition of viruses and other infectious agents, including indirect methods such as serologic and allergic reactions, should be applied in the study of rheumatoid arthritis. The methods which will disclose its cause may not be known as yet and will be found only by trial.

THE ENDOCRINE FACTOR

The possibility that rheumatoid arthritis is fundamentally an endocrine abnormality has not been demonstrable by clinical, laboratory or pathological measurements at our disposal. Extensive studies of the various endocrine systems of patients with rheumatoid arthritis have not revealed any constant abnormality. Physical characteristics are usually within normal limits except for emaciation and in some cases pigmentation similar to that seen in Addison's disease. The sex and age distributions, although suggestive, have not provided a clue. Studies on metabolic phenomena reflecting hormonal disturbances show no constant abnormalities that can be interpreted as significant. The rheumatoid patient is often in negative nitrogen, calcium and phosphorus balance, but these metabolic alterations can be corrected without influencing the disease. Occasionally such patients exhibit electrolyte disturbances, such as the inability to retain sodium, but usually the serum and urine electrolytes are normal. A decreased sugar tolerance may exist, but this also occurs in other chronic diseases. Little is known about fat metabolism except that cholesterol and cholesterol esters are not markedly abnormal. In our experience the 17-ketosteroid urinary levels are often low but can be within normal limits, and the urinary reducing steroids are not significantly changed. Adrenal cortical response to adrenocorticotrophic hormone and adrenaline is usually normal, and thyroid dysfunction has not been satisfactorily correlated with this disease.

Histological examination of the pituitary, thyroid, parathyroid, pancreas, adrenals and gonads by classical histological methods has not been revealing. It should be recognized that chronic debilitating disease of any nature can be associated with certain manifestations of endocrine dysfunction, and that when such phenomena do occur they are probably of secondary importance. The relationship of rheumatoid arthritis to the numerous clinical endocrinopathies requires additional study; thus far there is no evidence that it

is anything more than coincidental. Of particular interest are the endocrinopathies involving the adrenal gland. To our knowledge active rheumatoid arthri is has not been unequivocally demonstrated in either Cushing's disease or untreated Addison's disease, but our information is incomplete and inconclusive.* Since the activity of rheumatoid arthritis is suppressed by cortisone it is unlikely that Cushing's disease and rheumatoid arthritis would coexist. Recently it has been suggested that the adrenogenital syndrome represents a defect in the individual's ability to produce carbohydrate-active steroid (Bartter *et al.*, 1950). It is of interest that none of the three patients studied at the Massachusetts General Hospital had rheumatic disease. The postoperative remissions of rheumatoid arthritis, and perhaps the remissions of pregnancy, suggest an alteration of this disease by changes in adrenocortical function; however, these phenomena alone have little or no etiological significance.

CORTISONE AND ACTH

With the exception of the adrenocorticotrophic hormone and cortisone, exogenous hormones have failed to affect appreciably rheumatoid arthritis. It has been claimed that many of these agents have beneficial effects but none, including œstrogen, testosterone, progesterone, deoxycorticosterone, pregnenolone, anterior pituitary substances, chorionic gonadotrophin and insulin in doses used to date, has been shown basically to affect the disease. The profound effects of cortisone and ACTH are well documented (Hench *et al.*, 1950). Evidence accumulated thus far indicates that they do not eradicate the disease; nor is the exact manner known in which these hormones hold rheumatoid arthritis in abeyance. They have been reported to diminish inflammatory processes resulting from formalin and inflammation due to hypersensitivity (Selye, 1949; Gross, 1950). Experiments pertaining to connective tissue repair have revealed that large doses of adrenocorticotrophic hormone and cortisone inhibit the formation of granulation tissue (Ragan *et al.*, 1949; Plotz *et al.*, 1950) and the spreading of dye (T-1824) in the skin with or without added hyaluronidase (Winter and Flataker, 1950). The inhibition of granulation tissue is of great interest, but any relationship to the pathogenesis of rheumatoid arthritis is not apparent. Since the spreading phenomenon has been shown to be inhibited by other steroids which do not alter rheumatoid arthritis, the results with adrenocorticotrophic hormone and cortisone are of doubtful etiological significance. There is no evidence at present to show that rheumatoid arthritis results from a temporary or long-standing cortisone deficiency. Furthermore, the theory that the adrenogenital syndrome results from an inadequate production of carbohydrate-active steroid would indicate that such a defect would in all probability lead to virilism, which we know does not occur in rheumatoid arthritis. The alterations in electrolyte and protein metabolism under the influence of

* A well-documented instance of rheumatoid arthritis and Addison's disease is reported by Perera and Ragan (1950). It is of interest that the arthritis was controlled with small doses of cortisone.

cortisone can be dissociated from its anti-rheumatic effect. The alteration in carbohydrate production and utilization in relation to the anti-rheumatic factor has not been well elucidated, but the evidence available indicates a dissociation (Lukens *et al.*, 1950). It is probable that the beneficial effects of ACTH and cortisone have no specific relationship to the ultimate cause of rheumatoid arthritis, but certainly indicate the manner in which the body can at least profoundly influence the nature and severity of the disease. The fact that these hormones can have an equally beneficial effect on inflammatory lesions of known etiology (beryllium poisoning) seems singularly important (Kennedy *et al.*, 1950).

SELYE'S THEORY OF ADAPTATION

One could devote considerable space to Selye's concept of the alarm reaction and the diseases of adaptation and its significance in the etiology of rheumatoid arthritis (Selye, 1944, 1946, 1949, 1950). He has postulated that stresses or damaging stimuli, mediated through the pituitary, cause the production of adrenal hormones which are of importance in maintaining hæmostasis. He also states that through this same mechanism overproduction of the hormone regulating electrolyte equilibrium can result in rheumatic disease. The original experimental work supporting this hypothesis was the production of arthritis in rats with large doses of deoxycorticosterone under various experimental conditions, including a high sodium intake. He suggested that rheumatoid arthritis was due to repeated stresses with an excessive and damaging production of salt hormone. Inasmuch as the stress was thought to be mediated through the pituitary by the production of adrenocorticotrophic hormone, the striking improvement of rheumatoid arthritis with this hormone made it necessary to revise the hypothesis. He suggested subsequently that salt hormone, produced by the adrenal under stress, is influenced by some other pituitary substance and that ACTH alone produces predominantly 'gluco-corticoids' which are anti-rheumatic (Selye, 1949a). The salt hormones, or 'mineralo-corticoids', not only produce the arthritis but may have an additional deleterious effect by diminishing the output of 'gluco-corticoids' and antagonizing them peripherally. Our chief objection to the Selye concept is that it is based on an experimental arthritis which is in no way related to rheumatoid arthritis and which we have not been able to reproduce. In our own experiments deoxycorticosterone acetate in large doses, a 'mineralo-corticoid', does not aggravate rheumatoid arthritis even when considerable salt retention occurs, and the beneficial effects of cortisone are not altered by the simultaneous administration of deoxycorticosterone. Furthermore, salt retention does not seem to alter the effectiveness of adrenocorticotrophic hormone. These observations on patients are not in accord with the hypothesis offered by Selye.

CONCLUSION

Rheumatoid arthritis is essentially an inflammatory disease in which neither

the inciting agent nor the pathogenic mechanism is known. The inflammatory process could be initiated by a micro-organism, a harmful metabolite, a damaging exogenous agent, a metabolic degradation of one of the connective tissue components or the production of a defective connective tissue component. The complexity of the inflammatory response may be accentuated by local secondary reactions and perhaps by more remote metabolic phenomena. It seems apparent that the nature and the severity of the inflammatory process can be influenced within the individual by a mechanism which at least may be related in part to the pituitary-adrenal system. Whether some of the systemic manifestations of rheumatoid arthritis can evolve through this or other endocrine systems, particularly pigmentation, cessation of growth and alteration of menses, and a decreased excretion of 17-ketosteroids, is not known. There is no evidence that hypofunction of the adrenals plays a part in initiating the inflammatory process of rheumatoid arthritis or that adrenal hormones can completely suppress it. The adrenocorticotrophic hormone or cortisone-induced remissions of rheumatoid arthritis do not seem to be specific, for these hormones play a similar rôle in other inflammatory diseases, such as beryllium poisoning and certain hypersensitivity states.

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THE BEARING OF RECENT ADVANCES ON THE ETIOLOGY AND TREATMENT OF RHEUMATIC FEVER

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Advances in knowledge concerning the nature of a disease have in the past seldom led directly to advances in its treatment; preventive measures have often been immediately improved, but only in the long run usually has the sick patient benefited. There is a time lag during which we have to reorient our approach. On the other hand, advances in treatment, often of an empirical origin, have on occasion provided immediate clues to the nature of the disease. These generalizations are well illustrated in the field of rheumatism.

THE HÆMOLYTIC STREPTOCOCCUS

In rheumatic fever the most important advance of the last twenty years has been in the etiological sphere—the growing recognition of *Streptococcus hæmolyticus* Group A as the causative organism, the prime factor, not exclusive of other factors, but without which the disease would not exist. Up to 1931, an authoritative monograph on 'The Rheumatic Infection in Childhood' could be written without anything more on bacterial causes of the disease than a citation of Poynton and Paine's discovery in 1900 of the 'diplococcus of rheumatism', and vague speculations about a virus or a parasite: 'Recent advances in rheumatism', by Poynton and Schlesinger, published in the same year (1931), devoted 13 pages to the streptococcal theory, in which the whole emphasis was on either *Streptococcus viridans* or a non-hæmolytic streptococcus. Since then, due largely to the work of Homer Swift and his team at the Rockefeller Institute, and Alvin F. Coburn (1939, 1949) at the Presbyterian Hospital, both in New York, the prime rôle of β-hæmolytic Group A streptococcus (abbreviated to Gp.A, H.S.) has become evident. Perhaps the most important of the techniques employed has been the antigenic analysis by means of which Griffith and Lancefield were able to subdivide the group of organisms into over 40 different types. Accepting the rôle of Gp.A, H.S. (and there are still a few who reject it as non-proven), the problem is primarily why some people, particularly children in the lower income groups, react to Gp.A, H.S. infection in a different way from the general population, among whom it is widespread and endemic. The latter fact is well shown by the increase with age of serum titre of antistreptolysin O, and antihyaluronidase, which rises from a value of 1:1 at the age of six months to 1:512 at puberty. A great deal of work has

been done both on the properties of the organism and the reactions of the host, and it appears that first and foremost the determining factor is not due to a Gp.A, H.S. organism of a particular type or with particular properties, so far as they are known: thus among a group of patients known to be susceptible to rheumatic fever (that is, having previously suffered an attack of rheumatic fever some years before) a given type of Gp.A, H.S. will cause an attack of rheumatic fever in one person and not in another, despite a similar rise in antistreptolysin titre. Whilst the antistreptolysin titre and other indices of antibody responses to infection (such as antihyaluronidase, antifibrinolysin, antideoxyribonuclease) are on the average perhaps raised for slightly longer, or reach a somewhat higher level in the cases which develop rheumatic fever than in those which do not, in the individual there may well be absolutely no difference in these indices of infection between a rheumatic fever case and one suffering from simple tonsillitis. Rheumatic fever, it seems, may be due to a number of specific host-parasite relationships: it seems possible that these host-parasite relationships change as the body adds to its experience of streptococcal antibody formation.

Some recent work by Murphy and Swift (1949) on rabbits has shown that a rheumatic fever-like illness can be produced by inoculation subcutaneously of small doses of streptococci, followed a few weeks later by a similar small dose of a different type of this organism. After several of these inoculations, myocardial and valvular lesions develop which closely resemble the human lesion and are not found in control animals. The rabbits may even develop heart failure with a high sedimentation rate, and may die. It seems from Rothbard's work on the anti-M antibody, that type specific immunity develops after infection with a particular M-type: according to this theory rheumatic fever will occur only with successive infections due to different types. In summary therefore it seems possible from this work (which is built upon, and fits in with, numerous other observations of the past twenty years) that it is a sequence of different types of streptococcal infection in a susceptible child which brings about the illness we call rheumatic fever.

The factors which determine susceptibility are also unknown, but in some way they are related to poverty. Daniels found in his survey of Bristol families in 1942 a striking correlation with both the net income and the number of rooms per head in the family. It is difficult to determine any more closely whether poor nutrition contributes to this or whether, as seems at the moment most likely, bad ventilation and overcrowding leads to increased numbers of different Gp.A, H.S. infections. A genetic factor has received a good deal of attention from Wilson (1940, 1944) and others: she concludes that there is a recessive trait responsible for this disease, having shown that there is a greater likelihood of rheumatic fever if this has been present in one or, even more, in both of the parents. As always, it is difficult to avoid environmental factors in this analysis, but the family of prosperous farmers published in 1943 by Pickles, with 23 out of 53 descendants affected by rheumatic fever or rheumatic heart disease, is a powerful argument in favour of some inherited factor.

THE WIDER CONCEPT OF RHEUMATIC FEVER

During the 1939-45 war there were large numbers of young men herded to-

gether in closely packed groups and under optimum conditions for spread of epidemics. This presented an unparalleled opportunity for investigating the epidemiology of the disease, and full advantage was taken of this, chiefly in America, but to some extent in this country also. Publications by the American Commission on Acute Respiratory Diseases (1946), by Rantz and his group (1947), by Coburn (1939, 1949), and by Quinn (1948), and in the British Isles, by Green (1941, 1942), and Thomson and Glazebrook (1942), and others, have led to a much wider concept of rheumatic fever. In epidemics of sore throat due to Gp.A, H.S. it was found that besides those who ran a straightforward short course and those who developed suppurative complications such as otitis media, there was also a group which suffered from *non-suppurative* complications, including classical rheumatic fever. There was, however, a wide variation in this 'post-streptococcal state', as Rantz (1947) called it, or 'streptococcosis', ranging from a prolonged recovery with a high erythrocyte sedimentation rate lasting longer than the others, to cases which showed minimal and transient changes in the electrocardiogram about the tenth day, or to those who showed some slight fever at this time and then recovered without any of the florid manifestations associated in the textbooks with the names of Ballonius and Bouillaud. It seems probable therefore that following hæmolytic streptococcal infection, whilst the majority of people get better without any complications, a few develop rheumatic fever, and in between these two extremes there is a complete range of variously affected patients. Perhaps therefore in this sense it might be correct to talk of a 'touch of rheumatic fever'.

PREVENTION OF RHEUMATIC FEVER

Arising directly out of the growing certainty that rheumatic fever was invariably a post-streptococcal disease, came the first essays towards its prevention. This would not have been practicable before the discovery of sulphonamides and penicillin, but as antibiotics began to be used to control the infection, it was a logical step to use them in the prophylactic sphere: this was first done simultaneously in 1939 by Thomas and France, and by Coburn and Moore. The evaluation of such prophylactic methods is extremely difficult, and there is still considerable argument as to how effective these methods are for domiciliary use, what is the best method of prophylaxis, and how undesirable side-effects can be avoided. Evidence seems to be accumulating that given under standard and controlled conditions in hospital, such prophylaxis is effective; epidemics of sulphonamide-resistant hæmolytic streptococcal infections have occurred, however, on a large scale (Coburn, 1949) and penicillin therefore seems the more effective of these antibiotics for mass prophylaxis. The frequency of complications also seems less, even if the cost is more: Pitt Evans (1949), confirming the work of American and Australian authorities on oral penicillin, has had satisfactory results with a daily dose of 200,000 units of calcium penicillin in 5 per cent. glucose, three-quarters of an hour before breakfast. The difficulties of main-

taining this medication in the home are many, but it may prove to be a desirable measure for those children who have once suffered an attack of rheumatic fever and who therefore are susceptible to further attacks up to the age of puberty. After puberty the possibility of a further attack becomes much less, as Wilson and Lubschez (1944) have shown.

Another recent approach to this problem utilizes the latent period following tonsillitis before an attack of rheumatic fever supervenes. Massell and others (1948) claim that penicillin given early and in large amounts, e.g. 300,000 units of crystalline procaine penicillin G suspended in peanut oil containing 2 per cent. aluminium monostearate, injected intramuscularly on admission, repeated in forty-eight hours, and 600,000 units at ninety-six hours from admission (Denny *et al.*, 1950) soon after the onset of the sore throat, will not only decrease the antibody response, as Loge and Kilbourne (1948) had shown, and eradicate the hæmolytic streptococcus from the throat, but will also prevent subsequent rheumatic fever in a number of susceptible cases in which it would otherwise have occurred, i.e., after 50 per cent. of infections. The evidence of earlier observations is in contradiction to this last point (Weinstein *et al.*, 1950), but support for it has been adduced in a controlled study on a large scale by Denny *et al.* (1950). There is no evidence that penicillin is of any value *during* an attack.

DEVELOPMENTS IN THE TREATMENT OF ESTABLISHED RHEUMATIC FEVER

There are certain recent 'developments' in the treatment of established rheumatic fever which at any time may become 'advances', and possibly very important ones, but which at the moment exist as claims waiting to be confirmed. They will be mentioned briefly here.

(1) *3-hydroxy-2-phenyl cinchonininic acid*, 20 to 40 mg. per kg. body weight per day, has been claimed to have a high degree of efficacy, not only in animal experiments (Marshall, Bearborn and Blanchard, 1950), but also in rheumatic fever.

(2) *Sodium gentisate* (8 to 12 g. daily) has been claimed by Meyer and Ragan (1948) to be as effective as salicylates but without any of their toxic effects (see also reports by Camelin and Schaefer, and others, 1950).

(3) Massive dosage with *ascorbic acid* (4 g. daily) has been claimed by Massell and others (1950), from the Hospital of the Good Samaritan, Boston, to be highly effective in the acute phase.

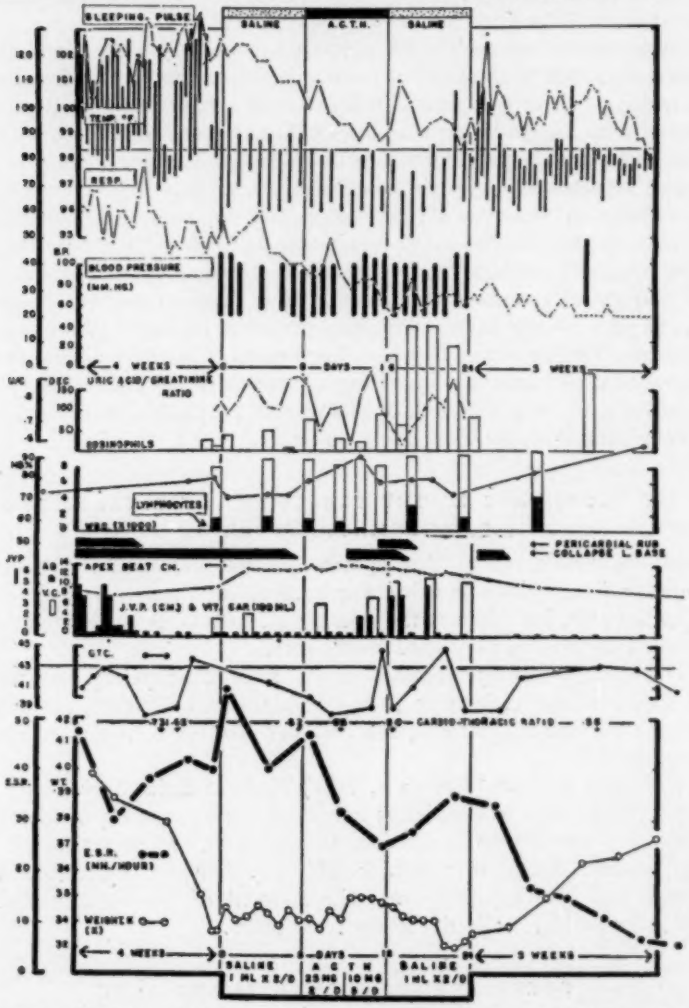
CORTISONE (COMPOUND E) AND ACTH

The most dramatic advance in the treatment of the established attack is of course the discovery by Hench and his colleagues (1950) at the Mayo Clinic of the action of cortisone and related compounds on the acute phase of rheumatic fever. There is no doubt at all that ACTH and cortisone given in adequate amounts act rapidly and effectively on the inflammatory process

CHART SHOWING COURSE OF RHEUMATIC FEVER ON ADRENOCORTICOTROPHIC HORMONE

Case E.V. aged 12½ years. Rheumatic fever 1 week before admission, following sore throat 2 weeks previously. Previous attack nine months ago (1st attack).

Examination: Mitral and aortic diastolic murmurs, arthritis, fever, pericarditis.



Note that the time scale doubles during the ACTH and saline periods. There is some improvement during the first saline period, a marked improvement in the ACTH period, and a partial relapse in the following saline period. Eosinophils were low to start with and relapsed following cessation of ACTH treatment. During the period of ACTH treatment lymphocytes fell, there was a slight gain in weight, and pericardial rub present on entry returned and disappeared soon after. The patient was left with heart only slightly larger than normal, with aortic and mitral diastolic murmurs and some mitral regurgitation.

in this disease, as in most other diseases involving the process of repair. There is still considerable uncertainty and even some measure of disagreement, however, on its exact status *vis-à-vis* salicylates, and so, before discussing the details of hormone therapy, we should do well to remind ourselves, first, that the aim of treatment is to prevent cardiac damage; secondly, that the criteria for assessment of such prevention are difficult to establish, and entail a long-term detailed study of comparable treated and control groups; thirdly, that such a study is not available either for bed rest or for salicylates, the two most important present-day weapons; and fourthly, that after 75 years it is still not known how salicylates work, nor has the undoubted therapeutic action of salicylates thrown any light on the etiology.

Following the discovery of the effect of cortisone and ACTH in rheumatoid arthritis, it was a logical step to try them in rheumatic fever, and Hench (1950) has since reported 8 such cases, with disappearance of fever in one to six days, and of arthritis between two and eleven days. There was a decrease in the erythrocyte sedimentation rate and pulse rate and other signs of activity. Thorn and Bayles (1949) have also reported cases from Boston with a similar result. These early results were preliminary communications, however, and, as the authors admitted, were open to the objection that a number of rheumatic fever cases show spontaneous subsidence of activity within the first week after admission to hospital. Therefore until a large number of cases became available, it was thought that perhaps the most valuable investigation that could be done in this country as a preliminary step and with the very small quantities of ACTH which were then at our disposal (due to the kindness of Dr. Tindall of Organon Laboratories Ltd.) would be to study the effect of this substance on the chronically active rheumatic fever subject. We selected for study patients who had had at least four weeks of continuous rheumatic activity as judged by various criteria, including a raised sedimentation rate. After a preliminary control period, ACTH was given in divided doses to a total of about 40 mg. per day for eight days. (A full account of these findings is to be published shortly). The first point that emerged from this work was that in their response to ACTH children with rheumatic fever differ in no way from normal children. There is a normal eosinophil fall and in some cases a rise in the urinary uric acid creatine ratio, with a rise in 17-ketosteroid excretion. It appears that there is no qualitative failure on the part of the adrenal gland to react to stimulation. Indeed, in the most severe cases of rheumatic fever the initial eosinophil count may be extremely low, down to below 1 per c.mm. (using Randolph's [1944] total cell count method), even when there is a leucocytosis suggesting that there is a spontaneously high degree of adrenal activation due to the disease. In all cases on ACTH there is a dramatic fall of temperature, and usually of pulse rate, which stays down and remains down for as long as the drug is given. Arthritis disappears during the first day, and the patient experiences a remarkable feeling of well-being. The sedimentation rate falls towards normal, reaching this level

after about eight days; following this short eight-day treatment period, in most cases it tends to rise again.

We have not observed any striking effects on the rash of rheumatic fever (erythema marginatum) within this period of treatment, nor on the nodules: biopsy of the latter showed little difference between specimens taken before and at the end of treatment. There was a tendency to retain water and chloride during the period of treatment, with in some cases an increase of weight of over 1 kilogram. Even in cases with congestive failure, however, little visible increase in œdema has been noted. It seems desirable in all patients in whom the heart is affected and who are to be treated with these compounds that they should be kept on a low-sodium diet, since this will decrease the tendency to retention and subsequent congestion. The heart itself, in the chronically active case, shows little sign of improvement during such short courses. Its size remains unaltered; the vital capacity and the jugular venous pressure show little significant change. Electrocardiograms have shown in some cases a decrease in the PR interval; in others a slight increase in the length of the corrected QT interval, falling to normal after stopping therapy. Pericarditis has been reported by Massell and others (1950) to disappear while on ACTH. In other cases a pericardial rub has appeared for the first time while on treatment.

It seems probable that these hormones should be given for a considerably longer period of time: I doubt whether much more is achieved in these cases of chronic activity given for such eight-day periods than can be done with aspirin. An ultimately more useful indication for giving these substances is perhaps the early case in which the endocardial inflammation is still in the reversible phase. It is well known that a small proportion of apical diastolic murmurs will disappear following subsidence of the rheumatic activity. Whether this proportion can be increased by early employment of these anti-inflammatory substances remains to be proved, but at the moment it seems a likely possibility and the best method of employing them in this disease.

Side-effects.—Over periods of eight days, side-effects of an undesirable nature are not prominent. It is only with more prolonged treatment that difficulties are encountered, due to the development of resistance or sensitization. Mild symptoms of Cushing's syndrome may sometimes be seen, such as the development of striæ, swelling of the face, acne or hirsutism. In some cases, potassium deficiency has developed leading to muscle weakness, and curable by giving potassium salts. Occasionally depression and, very rarely, mania have occurred. Glycosuria is uncommon. Most of these conditions revert to normal following the cessation of treatment. One danger should particularly be borne in mind, and that is the possible activation of a latent focus of tuberculosis. It is therefore necessary that a careful relevant history and chest X-ray should be taken. Relapses following treatment will, of course, not occur if the treatment has been continued for long enough. They may be severe following the sudden withdrawal of ACTH after a

short course, with fever, pericarditis and heart failure. They may be minimized by diminishing the daily dosage gradually before stopping.

CONCLUSION

The full extent to which cortisone and ACTH can usefully be employed in this disease is not yet certain. It is obvious that they have tremendous possibilities. Rheumatic heart disease accounts for a very large part of the chronic invalidity in the younger and potentially more productive age-groups. If it could be abolished by a relatively short period of treatment, this might well be considered more important than maintenance dosage in other diseases, until the time when supply catches up with demand. There are still dangers in the treatment, and until we have much more experience, it is better carried out in hospitals with laboratory control. When supplies improve it is hoped that the large numbers of investigations now being carried out will have borne fruit in the form of a clear and quantitative idea of the indications for, and the best mode of administration of, these powerful substances.

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THE FUNDAMENTAL TREATMENT OF RHEUMATOID ARTHRITIS

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The demonstration by Hench and his colleagues of the remarkable effects produced in rheumatoid arthritis by the administration of cortisone or ACTH has raised the hopes of the medical profession that a really effective method of treatment for this most disabling condition will soon be generally available. These hopes are not likely to be realized. Apart from the difficulties in the production of these hormones in large quantities, it has already become clear that their action is limited to a suppression of the symptoms of the disease. Remission lasts for only as long as administration is continued: on withdrawal, relapse is inevitable. The quantity required to meet the needs of the rheumatic population in these circumstances is likely to be far beyond that which can be produced in the foreseeable future. It has also become clear that an equally striking suppression of symptoms can be brought about by ACTH or cortisone in many other diseases of apparently unrelated etiology. Increasing demands will be made on the limited supplies available, for use in the elucidation of many fundamental problems in the field of medical research.

Those engaged in the study of the rheumatic diseases must remain deeply indebted to Dr. Hench, whose brilliant work led to the intensive study of the effects of these new hormones in cases of rheumatoid arthritis. A unique tool for research has become available. It may be justifiable to assume that by its application to fundamental problems, methods of treatment in rheumatoid arthritis may be profoundly altered, but for the present a note of caution must be struck. If the best functional results are to be obtained, the treatment of rheumatoid arthritis will continue to depend upon the conscientious application of less dramatic methods. It is the duty of the medical profession to clarify the position in the minds of their patients. Those physicians mainly concerned with the treatment of the chronic rheumatic disorders are already only too familiar with the anxious inquiries of patients and their relatives as to when supplies of the new hormone will be generally available. The hope of a dramatic cure can only lead to an attitude of impatience with present methods which require the fullest cooperation from the patient. It is well to bear in mind that neither corusone nor ACTH can replace articular cartilage or restore power to wasted muscles. The main purpose of this article will be to restate certain fundamental principles which must continue to govern the treatment of rheumatoid arthritis, even if

supplies of the new hormones become plentiful, or if they are replaced by the product of some brilliant chemical synthesis.

AIMS OF TREATMENT

In any disease of unknown etiology the aims of treatment are threefold. The first and most urgent must be the relief of symptoms. The second must be the improvement of the patient's general health in order to create optimum conditions for the mobilization of natural defence mechanisms, whether the disease be due to disordered metabolism, to an abnormal response to some unknown antigen, or to a breakdown in adaptation to environmental stresses. The third must be the conservation and restoration of function in structures damaged by the disease process. When these aims are applied to the problems of rheumatoid arthritis, treatment can be placed on a rational basis, and much of the empiricism of the past can be discarded. The prescription of a host of remedies the use of which is only sanctioned by outmoded conceptions of the etiology of the disease can no longer be defended. The victims of rheumatoid arthritis have been exploited for too long by the vendors of remedies the only virtue of which has been their innocuous nature. The medical profession, on the other hand, has repeatedly been guilty of sanctioning the use of methods of treatment, many of them not free from risk to the patient's health, without first obtaining evidence of their value by adequately controlled clinical trials. Experience with ACTH and cortisone has revealed the potential reversibility of the acute inflammatory component of the disease, and in future, remedies for which a specific therapeutic effect is claimed must be subjected to the most exacting investigation before being recommended for general use.

Before discussing methods of treatment, something must be said of the symptoms which they are designed to relieve. In rheumatoid arthritis the presenting symptoms are pain and stiffness of the affected joints, but in the majority of cases there is also evidence of a constitutional disturbance in the shape of excessive fatigue, loss of weight, anorexia, pallor, disturbances of the peripheral circulation, and occasionally, recurring febrile episodes. It is of some interest to note that in cases in which ACTH or cortisone has been given there is a rapid suppression of pain and stiffness in the affected joints. Function may improve dramatically in a few hours. It may be two or three days before the blood sedimentation rate begins to fall and the other signs of systemic disturbance begin to subside. This suggests that the adrenal corticosteroids act rapidly and directly on the inflamed structures in and around the joints. It would seem that the systemic disturbances may arise as a result of the primary inflammation. If this hypothesis be correct, it will have an important bearing on treatment. It will be of little value to concentrate on measures designed to alleviate constitutional symptoms if no attempt is made to control the function of inflamed joints. This point is well illustrated in figure 1.

This patient, who had suffered from rheumatoid arthritis for many years, developed an acutely painful and swollen left knee. The joint was completely immobilized in a plaster splint for 34 days. A walking plaster was then applied and the patient allowed to bear weight, but no active movement of the knee was permitted for a total period of 62 days. The blood sedimentation rate fell steadily, and there was a progressive improvement in the patient's general condition. On removal of the plaster and resumption of active movement the blood sedimentation rate rose rapidly, although pain and effusion only returned to a limited extent.

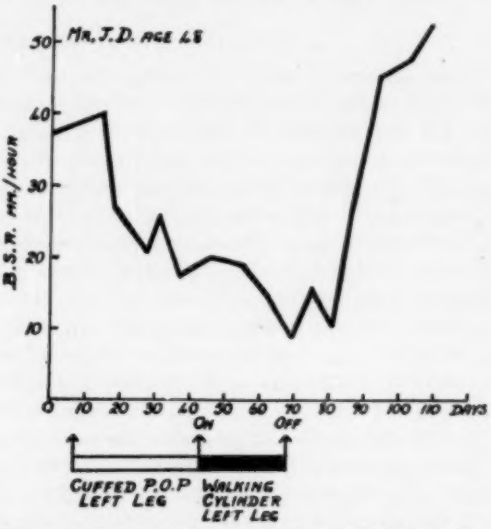

FIG. 1.—Effect on blood sedimentation rate of immobilization of acutely inflamed left knee in a man aged forty-eight.

It would therefore appear that the best results will be obtained, in respect of both constitutional and local symptoms, if methods of treatment are used which will control the inflammatory process in the joints. Viewed from this standpoint, marked constitutional symptoms are a clear indication of the need for treatment of the primary lesion in the joints.

In the past, the belief that the disease was due to some unknown infective agent led to an undue concentration on measures which it was hoped would raise the patient's resistance in some non-specific way. Great stress was laid on the eradication of septic foci. As a result, treatment of the affected joints received too little attention. It was considered sufficient to prescribe some form of physiotherapy in the hope that function would thereby be maintained until the active stage of the disease had been controlled by vaccines, protein shock, fever therapy or gold. In view of recent work, a new approach would seem justified, and it is proposed to outline a scheme of treatment based on the assumption that the correct treatment of the affected joints is of fundamental importance.

GENERAL MEASURES

The regime of treatment will vary according to the circumstances of each case. It may be said at the outset that all cases of rheumatoid arthritis, of whatever degree of severity, will benefit more from a period of rest in bed than from any other single form of treatment, provided that certain measures are adopted to counteract the possible ill-effects of immobility. Lack of beds

in hospital, inadequate accommodation and lack of supervision in the home, will severely limit the number of cases in which this is possible. In the active case with many joints involved and marked systemic upset there is no alternative to in-patient treatment, and these patients should have priority for admission to the available beds. The regime for this type of case will be discussed first.

Bed rest.—Removal of the load of function from the inflamed joints will go far towards fulfilling the first principle of treatment—the relief of symptoms. Pain and muscle spasm are largely conditioned by movement. The practitioner's responsibility, however, only begins with the prescription of rest in bed. Too often in the past it has ended there, with disastrous results in the shape of crippling deformities of the limbs. These arose from a failure to appreciate certain fundamental principles which will be discussed later. First, certain undesirable effects of uncontrolled rest must be mentioned. Physiologists have shown that bed rest of any duration has well-marked effects on the body as a whole: even in the healthy, physical efficiency deteriorates fairly rapidly; voluntary muscles lose bulk and power; and cardiac reserve diminishes. The deleterious effects of undiluted rest in patients whose physical efficiency is already markedly impaired is likely to be more profound. A compromise must be reached. While retaining the benefits of rest, every effort must be made to maintain and improve the general level of physical and cardiovascular efficiency.

The first point which requires attention is the *postural alignment* of the patient. The posture assumed by, or perhaps more commonly forced upon, the bed patient, is wholly unphysiological. During the day, he is propped up by numerous pillows into a semi-sitting position, often with inadequate foot support. The resulting grotesque alignment of the trunk and limbs is mercifully hidden by the bed-clothes (fig. 2). The spine is flexed throughout its

FIG. 2.—Posture in bed—bad alignment.

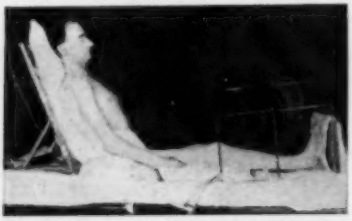

FIG. 3.—Posture in bed—good alignment.

length; the natural lumbar lordosis is reversed. The long back muscles are put on the stretch. The hamstrings are tight in this position, causing flexion of the knees—often increased by supporting pillows. The movement of the chest is restricted, and the abdominal muscles are relaxed. The feet are seldom properly supported and fall into the plantar-flexed position. Most of the common deformities which arise in rheumatoid arthritis can at least be attributed partly to periods of recumbency during which the joints were

allowed to remain for prolonged periods in the positions described. The effects on the respiratory and cardiovascular systems are difficult to assess, but unnecessary restriction of function must be undesirable.

Certain measures can be adopted which will largely counteract the ill-effects of rest in bed, while still securing its benefits for the arthritic patient (fig. 3).

(1) The mattress used should be firm, or fracture boards should be inserted.

(2) A firm back-rest with the minimum number of pillows should be in position during the day.

(3) A roomy cage with a padded foot-rest should be placed over the legs and feet, and anchored in position by straps. This should hold the feet at a right-angle.

(4) Pillows behind the knees should be forbidden (compare fig. 2 with fig. 3).

(5) At night only one firm pillow should be allowed.

(6) After the midday meal, patients should spend an hour resting flat, with a small pillow under the lumbar spine. A further fifteen minutes should be spent in the prone position with a pillow under the abdomen.

These simple measures will ensure reasonable posture in bed throughout the twenty-four hours.

In addition, the general level of physical and cardiovascular efficiency is maintained by the use of simple *exercises*. These maintenance exercises are designed to have their effect on the groups of muscles in the thoracic, lumbar, gluteal and abdominal regions. These comprise a large proportion of the total muscle mass. They are largely concerned with the maintenance of posture, and are relatively inactive in the recumbent position. Exercises which bring these important muscle groups into action, act as a stimulus to the general metabolism, make moderate demands on the respiratory and cardiovascular systems, and play an important part in maintaining the general fitness of the patient confined to bed. Accurate dosage is important, and the exercises must be supervised by the physician in charge of the case.

TREATMENT OF THE JOINTS

Immobilization.—It has already been suggested that correct treatment of the joints may be of fundamental importance in controlling both local and systemic symptoms in rheumatoid arthritis. In the past, great stress has been laid on the preservation of function by daily active and passive movements. Treatment has largely been influenced by the fear of bony or fibrous ankylosis. Experience has shown that the most common cause of limitation of movement in the affected joints is the formation of adhesions in the periarticular structures. True bony ankylosis is rare. In the belief that inflammation in joints will subside more rapidly if function is reduced to a minimum, it has become my practice to immobilize acutely painful joints in skin-tight plaster of Paris splints for periods varying from one to three

weeks. It has been found that pain and swelling subside more rapidly and completely than if the splints are removed daily for active movements. In many instances a marked increase in the range of movement has followed immobilization in plaster, and in no case has there been a serious or permanent diminution. It would appear that the danger of joints becoming stiff if splinted for any length of time has been greatly exaggerated. The principle of a period of complete rest seems to be of particular importance in the treatment of weight-bearing joints (fig. 1). Accurate splinting leads to a rapid diminution of pain and muscle spasm. Effusions are generally aspirated before splints are applied, but will subside with splinting alone. Splints are simple to make, and no elaborate equipment is required.

Ready-made plaster bandages are used, and applied directly to the oiled skin. In the case of the wrists and fingers, a posterior slab is applied and the splint completed

FIG. 4.—Hand and wrist plaster.

FIG. 5.—Wrist plaster

by encircling the fingers, which are held in the corrected position (fig. 4). A similar technique is used for the wrist alone (fig. 5). These splints are held in place by a crêpe bandage round the forearm, and can readily be removed. Figure 6 shows a splint which controls both the elbow and wrist. A useful method of ensuring complete immobility without the application of a full plaster (the removal of which with a plaster shears is often a painful process both for the operator and the patient) is illustrated in figure 7. A posterior plaster is made with the patient lying prone. This position ensures relaxation of the hamstrings and the correction of incipient flexion deformities of the knee. The splint is trimmed and re-applied with the patient in the supine position. Three plaster cuffs are applied over pads of felt in the position

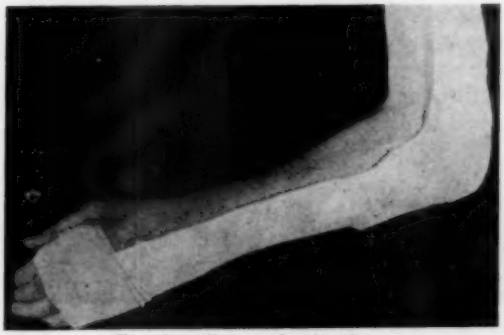

FIG. 6.—Elbow and wrist plaster.

shown. When the time for active movements comes, the cuffs are simple to remove, leaving the back splint intact for use as a rest splint.

(a) Position of patient.

(b) Application of back slab.

(c) Back slab in position.

(d) Application of cuffs.

(e) Plaster complete.

FIG. 7.—CUFFED LEG PLASTER

Drugs.—The combination of rest in bed and the application of splints to the affected joints will control pain in the majority of cases, and substantially reduce the need for analgesics and hypnotics, but these should be prescribed in adequate doses when necessary. Compound codeine tablets B.P., in doses of two tablets three times a day, will prove adequate in most cases. When sleep is disturbed, a drug of the barbiturate group (sodium amytal, 3 grains=0.2 g.) may be required.

PHYSICAL TREATMENT

The stage at which active movements should begin will depend upon the response to general and local rest. In the upper limbs, splints may be removed for meals and toilet from the start, but only when pain and swelling have begun to subside should active exercises and physiotherapy be prescribed. In the lower limbs, the period of complete immobility can be more prolonged, muscular function being maintained by static contractions of

thigh and calf muscles with splints in position. The patient should be taught these exercises and instructed to perform them at frequent intervals throughout the day. The general signs which indicate the time for more active treatment are a fall in blood sedimentation rate, improved appetite, a gain in weight, and an increased sense of well-being. The degree of improvement in the joints will depend to a large extent upon the presence or absence of irreversible damage, but diminution of swelling and periarticular tenderness indicates that inflammation is subsiding. This first phase of general and local rest will vary in duration, but in early cases a marked improvement will be evident in two to three weeks. However, the physician must be guided by the patient's response, and refrain from the use of over-strenuous methods of treatment until constitutional symptoms begin to improve and signs of active inflammation begin to subside.

Remedial exercises.—Having brought symptoms under control and created optimum conditions for the operation of the patient's natural defence mechanisms, the third object of treatment is to restore function to the damaged joints. Certain principles must be observed in the treatment of arthritic joints. The stability of a joint depends upon adequate muscular control of movement. A mobile joint with inadequate muscular control is particularly prone to injury. Such a joint often becomes the seat of a chronic effusion, and may be more of a disability than a joint ankylosed in good position. In rheumatoid arthritis, in which muscular wasting is a prominent feature of the disease, the affected joints must be protected from functional strain until bulk and power have been restored to the controlling muscle groups. This is especially important in the weight-bearing joints.

FIG. 8.—Weight and pulley exercises in bed—extensors of elbow.

The type of exercise which will restore power to wasted muscles is that in which the load on the muscle is progressively increased as its capacity for work improves. Simple weight and pulley circuits, attached to the patient's bed, are used for this type of remedial exercise (figs. 8, 9 and 10). The initial load is that which can just be moved by a maximum contraction of the muscle

FIG. 9.—Weight and pulley exercises in bed—flexors of elbow.

FIG. 10.—Weight and pulley exercises in bed—extensors of knee.

group under treatment. A stop is arranged in the circuit which ensures complete relaxation between lifts. Both the load and the number of lifts are increased as power improves. These exercises should be performed twice daily. The circuit illustrated can be used for any group of muscles, by altering the starting position of the patient. The application of heat before the sessions of exercise is useful in easing stiffness and improving the local circulation. Cold muscles are inefficient and liable to strain. When a stage is reached when the patient is considered fit to become ambulatory, as judged by the absence of effusions in the affected joints and improvement in constitutional symptoms, the time up is progressively increased and exercises are prescribed for the restoration of endurance. The stationary bicycle and rowing machine fulfil a useful purpose in this respect, but a wide variety of physical activities can be devised, suited to the age and sex of the patient.

Physiotherapy is used to supplement active forms of treatment. Wax baths are beneficial in reducing stiffness in the small joints of the hands and feet. Faradic footbaths may be helpful in initiating activity in the intrinsic muscles of the feet. Residual pain may be eased by radiant heat, infra-red rays, or short-wave diathermy. It must be clearly understood, however, that the value of passive forms of therapy is strictly limited. Power and stability can only be restored to damaged joints by skilfully graded activity. In cases of any duration, permanent damage will limit function, and patients must be warned that their activities must be kept within the tolerance of their joints.

Corrective splinting.—In certain cases, pain and swelling return in a knee or an ankle on the resumption of weight-bearing. In others, persistent muscular weakness makes walking difficult. In these patients a complete plaster may enable walking to be started (fig. 11, 12). Removal of the plaster in two to three weeks often reveals a marked improvement in the condition of the joint, and active exercises can be resumed.

FIG. 11.—Walking plaster for knee.

FIG. 12.—Walking plaster for ankle and foot.

In cases in which deformities have already become established, but movement is still present, correction can often be achieved by the application of serial plasters. The splint is applied in the position of deformity and left for one to two weeks. On its removal, the deformity can be partially corrected. A second plaster is applied in the improved position.

Full correction can often be achieved with a series of such splints. The cuffed plaster technique can be used for this purpose (fig. 7).

During this phase of treatment, occupational therapy is of great value, both from the physical and psychological point of view. It focuses the patient's interest on a constructive form of activity, and helps to restore manual skill and dexterity.

MEDICAL TREATMENT

Little has been said of the use of drugs and other remedies in the treatment of rheumatoid arthritis. This does not imply that these have no value, but emphasis has been placed on certain fundamental measures upon which, in my opinion, the success of treatment must ultimately depend.

Gold is of undoubted value, especially in early cases. Indications for its use and the technique of administration are described in many standard works on the rheumatic diseases. Recent work has shown that in cases in which hypochromic anæmia fails to respond to oral iron, as it often does in the active stage of rheumatoid arthritis, the administration of ***iron by the intravenous route*** may be of great benefit, both in raising the hæmoglobin level and improving the patient's general condition. A progressive fall in the blood sedimentation rate has often been noted following a course of injections. A total of 1 g. is given in three to five injections. Toxic reactions occur occasionally, but are mild and transient in the majority of cases.

A full and varied *diet*, supplemented by vitamin concentrates, is of great importance in underweight patients. It is of equal importance to get rid of excessive weight in obese patients by strict dietetic control, especially if the weight-bearing joints are affected.

AFTER-TREATMENT

When the patient has attained the maximum degree of improvement, certain clear-cut instructions must be given. The limits of physical activity must be clearly defined in those patients with significant residual disability. The physician will be guided by the functional status which the patient has attained during the second phase of treatment. Instruction should be given in simple home physiotherapy and remedial exercises. Splints should always be worn at night. This measure alone will prevent the development or recurrence of deformities. The social and economic situation should be carefully reviewed. Advice as to change of occupation should not be given lightly, but in young patients such advice may be essential if early breakdown is to be avoided. At this stage the services of an almoner, skilled in the handling of disabled patients, will be of the greatest value. Exploration of the home situation may reveal the need for minor, or even major, adjustments. It will be of little value to return a patient with a limited capacity for climbing stairs to the top flat of a tenement house.

Adequate follow-up is essential if the results of treatment are to be maintained in rheumatoid arthritis. Whatever the etiology of the disease, environmental factors at home and at work are of importance. Emotional stress and physical fatigue exercise an adverse influence in certain cases. Intelligent advice on such matters will often sway the balance in the patient's favour. Adjustments in the regime of treatment are required from time to time. Splints will require renewal. Over-optimism during remissions requires to be controlled, and depression during exacerbations can be lightened. The spacing of visits to the follow-up clinic will vary, but supervision should be lifelong.

CONCLUSION

The regime described will require modification to meet the needs of the individual case. Mild or early cases, without serious involvement of the weight-bearing joints and with minimal signs of constitutional disturbance, will not require admission to hospital. Splints can be fitted and treatment organized on an out-patient basis. In others, the help of the orthopædic surgeon may be required before a useful degree of function can be restored. The general practitioner has an all-important part to play in the day-to-day supervision and care of these patients. Plaster technique is not difficult, and can readily be acquired by the physician with sufficient interest and the desire to do the best he can for those in his care.

It is to be hoped that in the not too distant future the intensive research going on both in this country and America will lead to a knowledge of the etiology of rheumatoid arthritis, and put more effective remedies in the hands of the medical profession. Until then treatment must remain empirical, and reliance must continue to be placed on the application of those methods which have proved their value in the past.

ACTH AND RHEUMATOID ARTHRITIS

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Since the original report by Hench and his collaborators in 1949 upon the dramatic effects of cortisone and ACTH (adrenocorticotrophic hormone) in patients suffering from rheumatoid arthritis, a large amount of work has been done on the effect of these substances in this and other diseases, and many have been found to react with favourable clinical responses.

Whereas the rheumatoid process is affected directly by cortisone, by some means, as yet poorly understood, the effect of ACTH is an indirect one by virtue of its property of stimulating the adrenal cortex of the recipient to secrete steroid compounds akin to cortisone (Thorn and Bayles, 1949), and this fact cannot be over-emphasized. Since the whole range of activity controlled by the adrenal cortex appears to be stimulated by ACTH (Prunty, 1950), the effect on the recipient of the secreted steroids tends to be more complex than the effect produced by the administration of cortisone (Sprague *et al.*, 1950).

GENERAL THEORIES ON THE PART PLAYED BY ACTH IN RHEUMATOID ARTHRITIS

Deficiency replacement.—Since the disease responds to the administration of cortisone it is reasonable to suppose that this substance may be replacing the lack of physiological adrenal steroid. The response to ACTH would then be the result of increased amounts of this material released endogenously. The theory seems untenable on the grounds that rheumatoid arthritis is not associated with Addison's disease, and there is no convincing clinical or biochemical evidence correlating adrenal cortical insufficiency with the incidence of rheumatoid arthritis. The amounts of cortisone that are required for replacement therapy in Addison's disease are only approximately one-fifth to one-tenth of the therapeutic dose in rheumatoid arthritis.

Correction of perverted adaptation.—According to Selye (1949), rheumatoid arthritis is an example of a 'disease of adaptation', which may be defined as a perversion of the normal adaptation responses to stresses in the external environment. The administration of cortisone or ACTH restores an abnormal balance of adrenal steroid secretion towards normal. This theory requires clinical confirmation.

Abolition of allergic responses.—Cortisone and ACTH are highly effective in abolishing reactions to sensitizing stimuli. There is much evidence suggesting that rheumatoid arthritis is an allergic or sensitized response to an antigenic stimulus (Green, 1950), which is thought by some to be streptococcal. Analysis has shown, however, that there is no special incidence of

known allergic manifestations in patients suffering from rheumatoid arthritis (Empire Rheumatism Report, 1950).

MODE OF USE OF ACTH

ACTH is now commonly dispensed as a fine lyophilized powder which is extremely hygroscopic and may lose potency when in contact with the moisture of the air. It is stored at room temperature in sealed ampoules. Immediately before use it is dissolved in 1 or 2 ml. of saline and administered intramuscularly. These solutions require to be dispensed freshly before use, as the potency of ACTH rapidly falls off in neutral solutions. The potency of different batches of ACTH, supplied even by the same manufacturer, is liable to vary over a wide range. By common consent most preparations have been approximately assayed in terms of the preparation made several years ago by the Armour Co. in Chicago* (this preparation is designated 'LA-1-A'). Fortunately, this preparation has recently been adopted as the International Standard.

The *dosage* of ACTH employed in the treatment of rheumatoid arthritis has varied over wide limits, from as much as 200 mg. daily, to as little as 25 mg. daily, or even less. It is generally agreed that this larger dose is excessive. A reasonable average dose would appear to be 40 to 80 mg. per day.

The *frequency of administration* is of vital importance, as ACTH rapidly disappears from the body. Good results are obtained by administering one-quarter of the daily dose every six hours. Dispensed solutions of ACTH are kept in the refrigerator for a maximum period of eighteen hours. Even this method of administration, which is all the average patient can be expected to endure for prolonged periods, is grossly uneconomical in the use of ACTH. Continuous intravenous administration over a period of twenty-four hours enables the ACTH activity to be detected in the recipient's serum, and has been found to produce a response six to ten times greater than the administration of the same dose by the suggested regime (Prunty *et al.*, 1950). Preparations of ACTH are coming into existence which have a retarded absorption rate and may provide a more economical supply of the hormone to the patient over a period of time.

The optimum *length of time of administration* is a question that remains unsettled. The fact that relapse occurs on withdrawing the drug, dictates the necessity of prolonged therapy, whilst continuous therapy is more likely to lead to earlier manifestation of the undesirable results of the excessive physiological responses of the patient to the large amounts of hormone required. This question, and that of the undesirability of sudden withdrawal of the hormone, are discussed in more detail later.

Effectiveness of the administration of ACTH.—It has already been emphasized that the effectiveness of this substance is dependent upon the potential responsiveness of the patient's adrenal cortex, which in an oc-

*I am indebted to Dr. J. R. Mote, of the Armour Company, Chicago, for gifts of ACTH.

casional instance does not appear to be present (Thorn and Bayles, 1949; Elkington *et al.*, 1949). This becomes evident by the absence of a clinical response, and will be apparent earlier by the absence of the characteristic fall in the eosinophil count four hours after the first dose, which for this purpose may conveniently be one of 25 mg. of ACTH, or after twenty-four or forty-eight hours of the therapy. Confirmatory evidence may be obtained from poor responses in increase of urinary steroid excretion. Such findings may indicate a trial with increased dosage of ACTH.

CLINICAL EFFECTS OF ACTH ON THE ARTHRITIC CONDITION

Within a short time of the beginning of therapy, even within a few hours, the patient begins to experience a sense of 'well-being' which is usually accompanied by the development of a true euphoria. Articular changes are ushered in by a progressive decrease in pain and stiffness which may proceed throughout approximately the first week of therapy. Next there follows an increase in the freedom and speed of movement which, in the earlier stages at least, appears to be due to a decrease in these symptoms. There next follows a phase during which diminution of periarticular swelling and of effusion is apparent. In cases with flexion deformities it is not until several days or weeks have elapsed that obvious improvement in the range of movement which has been limited on this account may occur, and then the degree of improvement is often really surprising. Thus a fixed flexion of the digits of 60° may be reduced to one of only 10°, with accompanying improvement in the patient's grip and increased digital dexterity; the patient may, for instance, once again be enabled to play the piano. It is not to be expected that joints w' ich have become ankylosed as a result of severe changes in cartilage and bone will show such improvement. The amount of benefit, however, which may be obtained in chronic cases is indeed remarkable and has been attested by all with experience of cortisone or ACTH. An unhappy bedridden individual, in constant pain, may be restored to a reasonably happy, useful member of the household. Parallel with the articular improvement, other clinical effects are apparent. The fever in acute cases rapidly subsides, as also does the pulse rate, and the basal metabolic rate, if it has been raised, may decrease. Appetite improves noticeably. During more prolonged treatment a considerable diminution in the size of the rheumatic nodules is to be noted; and in those patients in whom accompanying psoriasis is present, this may be greatly benefited.

EFFECTS OF ACTH ON OTHER OBJECTIVE PHENOMENA

Sedimentation rate.—In general there is a progressive fall in this measurement, and often normal levels may be obtained. This fall can be delayed considerably, and not related to the improvement in symptoms and signs. According to Hench *et al.* (1950), this is an advanced and less easily reversible component of rheumatoid arthritis. Since larger doses of hormone

may be required to produce a normal sedimentation rate than adequate symptomatic improvement, the likelihood of undesired effects is enhanced if too much stress is placed on this determination. For this reason it is probably wisest to employ the smallest dose which will control the disease, and ignore the sedimentation rates.

White cell counts.—Total white cell counts may be expected to show an appreciable rise with effective doses of ACTH, and should not be interpreted as evidence of intercurrent infection. This change is accompanied by a polymorphonuclear leucocytosis and sometimes a lymphopenia.

Eosinophils.—In a normally responsive patient a marked fall in the level of eosinophils, as estimated by direct counting methods, should be observed; early and sustained depression of the level of the morning counts is useful confirmatory evidence of the patient's responsiveness to the hormone.

Red cells.—Anæmia is a frequent accompaniment of rheumatoid arthritis. Increase in red cells and hæmoglobin are sometimes found in these patients, but this observation is complicated by a tendency to a fall in the packed cell volume due to fluid retention (see p. 38). In this connexion reticulocytosis has been described by Thorn *et al.* (1950).

Plasma proteins.—In a proportion of cases of rheumatoid arthritis serum proteins are abnormal, usually due to increases in the globulin fraction, with a less marked decrease in the albumin level. The effect of ACTH is to reverse these abnormal changes.

Serum uric acid.—With prolonged administration of ACTH, Forsham *et al.* (1948) observed that the level of serum uric acid fell significantly in the human individual. This change is often found to occur in responsive patients with rheumatoid arthritis.

Urine steroids: (1) *17-ketosteroids.*—In many cases of rheumatoid arthritis the excretion level of these steroids appears to be low, whereas in the remainder of the cases they are normal (Hench *et al.*, 1950). This has also been my experience. After adequate response of the patient the level of 17-ketosteroids usually shows a significant increase after forty-eight hours' therapy. (2) *Reducing steroids.*—The estimation of these steroids affords a more delicate and precise index of adrenal cortical response (Brooksbank, Owen and Prunty, 1950), although this estimation is too laborious for widespread clinical use. A failure to observe a significant response after approximately five days' treatment may be taken as definite evidence of failure of the adrenal cortex to respond to the dosage of ACTH being employed. 17-ketosteroid and corticosteroid estimations afford the best objective criteria of the degree of adrenal cortical stimulation by ACTH.

Joint fluid.—Significant alterations in the synovial fluid have been noted by Clark, Roper and Bauer (1950), who found a fall in the cell counts and a rise in the viscosity of the fluid. This is associated with physico-chemical changes in the mucin present, and probably with the inhibiting effect of the adrenal steroids on hyaluronidase activity.

Response to streptococcal antigens.—Increases in the streptococcal ag-

glutination titre and antistreptolysin in rheumatoid arthritis have been reported and are not constantly reduced by ACTH therapy. These changes have not been studied nearly so extensively as the changes in the sedimentation rate.

Synovial biopsy.—Biopsies after treatment, especially in cases in which the effects of cortisone have been studied, show considerable resolution in the inflammatory infiltration of the tissue, and in the amount of papillary proliferation (Hench *et al.*, 1950).

Electro-encephalographic changes, characterized by increased amounts of slow activity, have been described during the use of ACTH.

UNDESIRABLE CLINICAL EFFECTS OF ACTH

Hitherto many of these effects have been classed as 'toxic' or 'side-effects'. In so far as these are, in many instances, enhanced physiological effects of ACTH, these terms would appear to be inappropriate (see also Sprague *et al.*, 1950). The phenomena discussed below have all been observed. It is still too early to make any accurate assessment of the exact incidence of these changes. For the present it is essential neither to underestimate their importance, nor to be discouraged by their possible occurrence. That they appear is a strong reason for continued close control of the patient under conditions where adequate laboratory facilities are available. The impression is most certainly gaining ground that they are more likely to be associated with too large a dosage, or too prolonged continuous usage of the hormone. This is a valid reason for compromising on dosage to produce the best clinical response, and not necessarily complete return to normal of all laboratory findings, which may in fact never be achieved.

Changes in the patient's appearance.—Quite a frequent alteration is the onset of fullness of the face, which if allowed to progress, assumes the typical '*moon facies*' seen in Cushing's syndrome. This may be accompanied by the development of *hypertrichosis* and, in rare instances, thinning of the hair of the scalp. Other features seen in Cushing's syndrome have been recorded, including purple *striæ*, *keratosis pilaris* and *acne*. Many of the patients treated for long periods may put on considerable weight, partly through increased appetite and a tendency to adiposity, and partly by reason of fluid retention, which is sometimes clinically manifest as *œdema*. In occasional instances *pigmentation* of the skin and nails has been observed. This may occur in cutaneous creases, and scars, and healing skin lesions. It is not apparently related to adrenal insufficiency.

Sexual function.—Some patients complain of alteration of the menses, which may become scanty, or complete amenorrhœa may develop. In men, diminution in libido has been noted. These effects would appear to be reversible after the cessation of treatment.

OTHER SYSTEMIC EFFECTS

Fluid retention and changes in electrolyte distribution.—Fluid retention often

occurs in patients treated with ACTH. It is usually indicated by the development of œdema, preceded by increase in weight, which may amount to several kilogrammes in a few days. This rapid gain in weight should be distinguished from a more gradual steady gain associated with increased appetite. Accompanying the fluid retention is a retention of sodium and chloride, and a decrease in the packed cell volume may be observed (Prunty, Forsham and Thorn, 1948). It is usual for a spontaneous diuresis to occur after withdrawal of ACTH, or sometimes even during its administration, with a concomitant loss of sodium and chloride. This fluid retention is often observed when adequate doses of ACTH are used. Owing to the fact that blood volume is increased, an undue strain may be placed on the heart of patients with myocardial impairment, and care must be exercised to avoid the occurrence of cardiac failure. Alterations in potassium metabolism may also present a hazard in this respect, since the occasional patient loses excessive amounts of potassium.

Blood pressure.—In patients with normal blood pressure, this is unlikely to be seriously disturbed. It is agreed, however, that in the patient with pre-existing hypertension, or glomerulonephritis, significant increases are likely to occur (Thorn *et al.*, 1950). In such instances the risk of inducing encephalopathy must be remembered.

Hyperglycæmia and glycosuria, although described with ACTH administration, have not so far been prominent findings in patients with rheumatoid arthritis. When diabetes mellitus is a complication, insulin requirement is increased during treatment, and may fall precipitately. To date, the long-term effects of ACTH on diabetes are insufficiently known to assess the risk to these patients.

Decrease of muscle strength.—This symptom is sometimes complained of in patients treated with ACTH for long periods. In many instances, this is probably related to the 'anti-anabolic' effects of steroids secreted in response to ACTH stimulation, which tend to be accompanied by nitrogen losses and increase of creatine excretion. A second factor that is of importance in a few cases, is excessive loss of potassium resulting in low serum levels of potassium. This, if sufficiently severe, is accompanied by typical alteration in the electrocardiographic pattern (Elkington *et al.*, 1949).

Mental changes.—The euphoria accompanying ACTH administration may be regarded as being physiological. It may be followed by increased mental activity, and the patients talk of experiencing profusion of thought. When this advances it causes sleeplessness. The reaction may give way to depression. In a case reported by Hoefer and Glaser (1950), a serious manic psychotic reaction ensued.

Effects on inflammatory tissue and infections.—Experimentally, ACTH has a definite effect in retarding the healing of wounds, and this has been observed to occur clinically at biopsy sites. Such an effect would be expected to increase the risk of a patient under treatment when exposed to infection. Furthermore, attempts to demonstrate increase of antibodies in the γ-

globulin protein fraction in human subjects injected with ACTH have been unsuccessful. On these grounds, reactions of patients to infections are likely to be atypical, and especially when the antipyretic and leucocytic effects of ACTH are also considered. Beck *et al.* (1950) described two patients who developed peritonitis while receiving ACTH, in whom the symptoms and signs were atypical, and the formation of fibrin and adhesions was less than expected. Bacteriæmia has also been found in the absence of classical signs of septicæmia. An infected bursitis in a case of rheumatoid arthritis under my care showed a definite tendency to flare-up during periods of treatment, and the same patient developed a small encysted pneumococcal empyema during therapy. Finally, the question has been seriously raised whether or not tuberculous infection may be exacerbated by the hormone, and the point needs careful watching until further data have been obtained.

SIDE-EFFECTS

The phenomena under this heading may be regarded as true 'side-effects' and are not concerned with the normal physiological activity of ACTH.

Local reactions to ACTH.—Firm, brawny swellings with overlying redness, which cause irritation, may rarely be seen at the sites of injection.

Sensitivity to ACTH protein preparation.—This is rarely seen, but may be induced by the occurrence or exacerbation of fever, or the development of urticarial lesions accompanied by intense irritation. In these circumstances, the use of antihistamine drugs is indicated.

Development of resistance to ACTH.—The true incidence of this phenomenon awaits determination since it depends upon prolonged use of ACTH. It is evidenced by the need for increasing dosage of ACTH to produce the expected chemical and physiological responses. It may be accompanied by increase of complement-fixing antigen in the recipient's serum (Elkington *et al.*, 1949; Hardisty, 1950).

Posterior pituitary contamination.—Most preparations of ACTH now contain only minimal amounts of posterior pituitary contamination. When present in significant amounts, this causes generalized pallor a few minutes after injection, an urge to defæcate, and uterine cramps.

CONTRAINDICATIONS TO THE USE OF ACTH

It can readily be appreciated from the foregoing that at the present time it is only possible to make tentative suggestions of conditions which contraindicate the use of ACTH. These may be summarized as follows:—

Myocardial insufficiency
Diabetes mellitus
Cushing's syndrome
Patients with marked 'tension states'
Tuberculosis
Severe renal disease

ADJUVANT THERAPEUTIC MEASURES WITH ACTH

Salt restriction.—In order to prevent the gain in weight and fluid retention, which have been emphasized to be a common accompaniment of the effects of ACTH, it is a good plan to restrict the daily intake of sodium chloride in the diet to low levels. The normal intake of salt by most persons is 5 g. or more per day. It is relatively easy to reduce this to 2.5 g. without the diet becoming too unpalatable. The table gives an example of the effectiveness of this procedure in a patient with rheumatoid arthritis:—

ACTH mg./day	No. Days	NaCl intake (g.)	Weight gain (kg.)	Clinical œdema
40	10	4·7	3	+
50	12	4·7	7	+++
40	10	2·3	0·5	0

Potassium administration.—To combat the occasional occurrence of excessive loss of potassium, 2 g. of potassium chloride may be given orally every day. This may be used prophylactically, or after falling levels of serum potassium have indicated its need.

Use of mercurial diuretics.—It is probably more prudent to prevent œdema than to allow it to occur, and then attempt to rectify the situation with mercurial diuretics. These drugs are liable to cause excessive losses of sodium when their diuretic effect coincides with that due to ACTH, and serious electrolyte disturbances may be induced.

Analgesics.—During ACTH therapy the patients' requirements for these drugs ultimately disappear, and the use of salicylates, for example, may be discontinued. Requirements in this respect form a useful ancillary measure of the effectiveness of treatment.

Physiotherapy.—It is of the greatest importance that this should be continued during the use of ACTH, for two reasons: first, it enables maximum advantage to be taken of the considerable improvement in movements which occurs at the joints, and ensures that these are mobilized to the fullest extent possible; secondly, it probably assists in combating any tendency to muscle weakness which is liable to occur as a result of administration of ACTH.

Stimulation of the anterior pituitary on withdrawal of ACTH.—If large doses of ACTH have been used during the course of treatment it is likely that the secretion of endogenous ACTH by the patient's pituitary will be in an inhibited phase. This would be reflected in an adrenal cortical activity in the patient which is less than normal. It is difficult to obtain corroborative evidence for the occurrence of such a phenomenon, but direct adrenal inhibition after the withdrawal of cortisone is manifest by decreased steroid excretions in patients so treated (Sprague *et al.*, 1950). In order to combat this theoretical pituitary inhibition it has been suggested (Thorn and Bayles, 1949) that at the time of withdrawal, adrenaline might be administered to stimulate the production of ACTH by the pituitary (Prunty,

1950). Whilst being theoretically desirable, the effectiveness of such a procedure is open to considerable doubt. In figure 1 the data are given showing the effect of intermittent adrenaline injection in a patient with acute rheumatoid arthritis studied in July 1949. It will be seen that although a considerable reduction was observed in the eosinophil count, no detectable increase occurred in the urine 17-ketosteroids or reducing steroids. It may be that

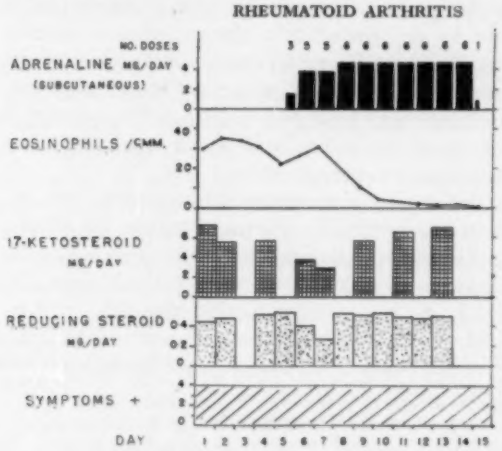

Fig. 1.—Effect of intermittent injection of adrenaline in a patient with rheumatoid attacks.

the amount of adrenal stimulation required to cause an eosinopenia is markedly less than that required to produce a significant increase in steroid excretions. The patient showed no symptomatic improvement whatever in her rheumatic condition, and was merely distressed by the effects of the adrenaline. This poor response is, in fact, compatible with those of Thorn and Bayles (1949), and of Dresner *et al.* (1950).

CONCLUSIONS

There can be no question that the majority of patients with rheumatoid arthritis show dramatic clinical improvement when treated with ACTH or cortisone. So far, but few patients have been treated for prolonged periods. Mild, undesirable effects are common, and the incidence of serious complications much less common. Thus, sixteen patients cited by Freyburg (1950) showed no serious complications; whereas Hench *et al.* (1950) had four instances of marked undesirable effects in 23 patients treated with cortisone and ACTH. The true incidence of these effects with prolonged treatment awaits appraisal, as does the expectation of continued benefit after the withdrawal of the hormone. Nearly all cases are reported to relapse completely in a few days to a few weeks, with few exceptions. Thus, one of Hench's patients maintained most of his improvement for as long as five

months. Little is known of the long-term maintenance requirements of these patients, but there is the possibility in some patients of tiding over the individual until spontaneous remission occurs.

Although the effects of ACTH on the pathological processes of rheumatoid arthritis are of the greatest fundamental importance, from the purely therapeutic standpoint it can only be regarded as a palliative measure. Its indiscriminate use in short courses only, without assured outlook for maintenance, should be deprecated in a chronic disease such as rheumatoid arthritis. Under these conditions all that is achieved is to restore a patient who has a chronic disability, and who has become adjusted to this, to a greatly improved state for a brief period of time. The effect of this procedure is merely to accentuate the difficulty of management of the patient after relapse, and has nothing to recommend it.

Meanwhile, the degree of improvement attainable with ACTH remains as an objective to be attained by alternative means. Its effect on the pathological process may assist in determining what these means are likely to be. It does not, apparently, strike at the cause of the changes, but only at the manner in which the body reacts to this stimulus. I may sum up in agreeing with Hench that for the present the use of ACTH and cortisone should be regarded as aids in 'an investigation in clinical physiology'.

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HORMONAL DISTURBANCES ASSOCIATED WITH RHEUMATOID ARTHRITIS AND RELATED CONDITIONS

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THE idea that certain of the endocrine glands may be in some way involved in the etiology of diseases of the rheumatic group is not a new one, and in the past clinical observations have suggested the possibilities that the thyroid, the pituitary, and the sex glands may be so involved. Recently, however, the striking discovery by Hench, Kendall and their co-workers (1949a,b) at the Mayo Clinic that cortisone or anterior pituitary adrenocorticotrophic hormone (ACTH) will alleviate the symptoms of rheumatoid arthritis and of acute rheumatic fever, has drawn particular attention to the adrenal cortex in this connexion.

The Mayo Clinic workers started with the working hypothesis, derived from the earlier clinical researches of Hench (1938) that the remissions of the symptoms of rheumatoid arthritis which occur during pregnancy and jaundice might be due to an 'anti-rheumatic factor X' arising from the adrenal cortex. This working hypothesis led them to the discovery of the dramatic effects of cortisone and of ACTH in this disease and in rheumatic fever, but it should be pointed out that they cautiously avoided any speculations upon the etiological rôle of the adrenal cortex in these conditions.

Although the Mayo Clinic work provided no definite evidence that the adrenal cortex is involved in the etiology of rheumatoid arthritis and related conditions, it is difficult, in view of other evidence of an indirect nature which is available, to avoid the suspicion that these diseases may at least be associated with some abnormality in the secretion or metabolism of the adrenocortical hormones. In this article an attempt is made to summarize and to review critically this indirect evidence.

SELYE'S THEORY OF THE ETIOLOGY OF THE RHEUMATIC DISEASES

Selye (1949a, 1950a) has recently suggested that an important etiological factor in the rheumatic diseases, and in certain other conditions regarded by him as 'diseases of adaptation' (Selye, 1949b), may be an imbalance between the principle(s) in the adrenocortical secretions regulating electrolyte and water metabolism—the so-called 'mineralo-corticoids' and those concerned in the regulation of carbohydrate metabolism—the so-called 'glucocorticoids'. Since direct evidence for the existence of any such 'imbalance' in the adrenocortical secretions in the rheumatic diseases is lacking, and since some of the assumptions made by Selye concerning the biochemical func-

tions of the active principles in the adrenal cortex cannot be accepted unreservedly, this theory must be discussed critically at some length.

In the course of their work on the rôle of the adrenal cortex in the adaptation of the body to various types of stress, Selye and Pentz, in 1943, observed that in unilaterally nephrectomized rats on a high sodium chloride intake, massive doses of 11-deoxycorticosterone acetate (DOCA) caused lesions in the heart and blood vessels similar to those observed in man in periarteritis nodosa, malignant hypertension and rheumatic fever. It was accordingly suggested that these diseases in man 'are, at least partly, caused by an abnormal (probably excessive) adaptive response of the adrenal cortex . . . '. The following year it was reported (Selye, *et al.*, 1944) that similarly prepared rats, if also adrenalectomized, thyroidectomized, or exposed to cold, often developed joint lesions after treatment with DOCA, which were said to resemble those seen in man in acute rheumatic fever. The authors stated: 'it appears that the rôle of the cold, thyroid or adrenal deficiency would be to favour a localization of the desoxycorticosterone acetate action in and around joints', and their tentative conclusion was as follows: 'The clinical and histologic similarity of the arthritis observed in our animals with that seen in the acute rheumatic fever of man suggests that the human disease may be a clinical manifestation of adrenal cortex hypertrophy'.

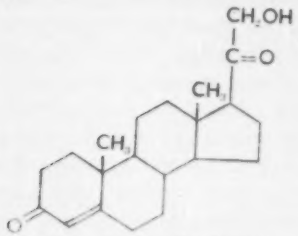
By 1946 Selye had developed his theory of the etiology of the rheumatic diseases and of certain other 'diseases of adaptation' a stage further. It is clear that at this time he was considering that the 'adrenal cortex hypertrophy' mentioned in his earlier work might involve an excessive secretion of 'mineralo-corticoids' with a 'DOCA-like' action, but no suggestion seems to have been made that the effects of such an abnormality in adrenal secretion might possibly be combated by the administration of a 'gluco-corticoid'.

Following the announcement in 1949 by the Mayo Clinic group of the effects of cortisone and of ACTH in rheumatoid arthritis and rheumatic fever, Selye (1949a) re-interpreted his earlier findings concerning the effect of adrenalectomy on the production of experimental arthritis by DOCA. He suggested that 'it was reasonable to assume that adrenalectomy sensitizes to the toxic effects of D.C.A. because it removes the source of endogenous gluco-corticoids and thereby predisposes to the development of a particularly unfavourable gluco-corticoid/mineralo-corticoid balance'. In support of this hypothesis he cited a number of earlier observations made by himself and his co-workers suggesting that certain of the effects on living animals of 'mineralo-corticoids' such as deoxycorticosterone are 'diametrically opposed to those of gluco-corticoids'. It may be noted, however, that this earlier work did not include any observations that 'mineralo-corticoid'-induced rheumatic lesions in animals could be cured by the administration of 'gluco-corticoids'. In the same communication Selye showed that an experimental 'arthritis' could be produced in rats by the injection of formaldehyde into the vicinity of the joints. This experimental arthritis, he found, could be aggravated by pre-treatment of the animals with DOCA and inhibited by cortisone or ACTH.

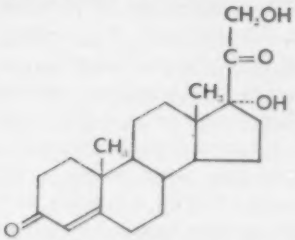
DISCUSSION OF SELYE'S THEORY

Selye's views upon the etiological rôle of the adrenal cortex in the rheumatic diseases (1949a,b) in man are based on the assumption that the adrenal cortex secretes two distinct types of 'life-maintaining' hormone, the physiological rôles of which are primarily the regulation of electrolyte metabolism and of carbohydrate metabolism, respectively—the so-called 'mineralo-' and 'gluco-corticoids'. However, the pharmacological evidence that the active 'life-maintaining' compounds present in the gland can be so classified is by no means completely satisfactory, whilst evidence that such pharmacological differences as have been observed between the different active compounds have any physiological or biochemical significance is lacking.

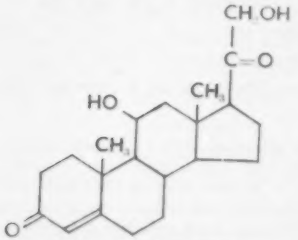
Six different pure crystalline steroids (I-VI), which are active in prolonging the lives of adrenalectomized animals, have so far been isolated from



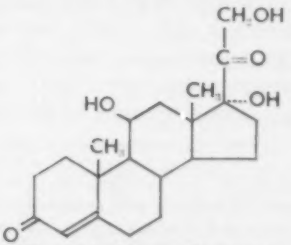
I.—11-deoxycorticosterone



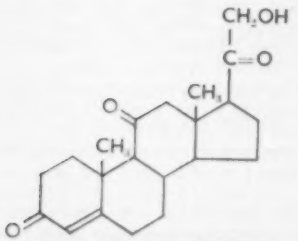
II.—11-deoxy-17-hydroxycorticosterone



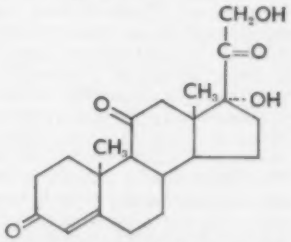
III.—Corticosterone



IV.—17-hydroxycorticosterone



V.—11-dehydrocorticosterone



VI.—11-dehydro-17-hydroxycorticosterone (cortisone)

adrenal glands. After as complete removal as possible from an adrenal extract of these active steroids and of various inactive ones, an 'amorphous fraction' remains which possesses a not inconsiderable proportion of the original 'life-maintaining' potency of the extract. So far as I am able to judge, Selye (1950b) seems to hold the view that these active compounds can be divided fairly sharply into two groups as follows:—the 11-deoxy compounds (I and II) and the unknown compound(s) in the 'amorphous fraction', active in regulating electrolyte metabolism but inactive in regard to carbohydrate metabolism; and the 11-hydroxy and 11-keto compounds (III-VI), highly active in regard to carbohydrate metabolism, but much less active towards electrolyte metabolism. This view does not seem to be entirely in accord with the published data on the activities of these compounds in

pharmacological tests, and in fact would seem to be an over-simplification of a rather complex state of affairs.

There seems to be no doubt that 11-deoxycorticosterone (I), usually tested in the form of its acetate (DOCA), and the 'amorphous fraction' are both highly active in causing sodium and chloride retention, but are virtually inactive in short-term *in vivo* tests involving effects on carbohydrate metabolism, such as glycogen deposition in fasted adrenalectomized animals, inhibition of the hypoglycæmic action of insulin, or production of glycosuria. There also seems to be no doubt that the 11-hydroxy and 11-keto compounds (III-VI) are active in short-term *in vivo* tests involving effects on carbohydrate metabolism, but are much less active than deoxycorticosterone as 'mineralo-corticoids'. The facts might appear to justify to some extent the classification of the 11-deoxy compounds on the one hand, and the 11-hydroxy and 11-keto compounds on the other hand, as 'mineralo-' and 'gluco-corticoids', respectively. However, an examination of other evidence suggests that even from a pharmacological standpoint such a classification may not be entirely justified.

First, an examination of the available pharmacological data on 11-deoxy-17-hydroxycorticosterone (II), which Selye (1950b) describes as a 'mineralo-corticoid', suggests that its status as such is somewhat dubious. It seems clear that this compound is inactive in short-term carbohydrate metabolism tests (Ingle, 1941; Reichstein and Shoppee, 1943), and is active in causing sodium and chloride retention in the normal dog (Clinton and Thorn, 1942). It is also feebly active in causing diuresis in the unilaterally nephrectomized rat (Masson, Corcoran and Page, 1950). However, Clinton and Thorn showed that its sodium- and chloride-retaining potency was significantly lower than that of the 'gluco-corticoid' corticosterone (III). It might therefore be said that its claim to be called a 'mineralo-corticoid' rests more upon its apparent lack of 'gluco-corticoid' activity than upon its possession of weak activity towards electrolyte and water metabolism.

Secondly, Verzár and his co-workers (Montigel and Verzár, 1943; Sass-Kortsák, Wang and Verzár, 1949) have shown that contrary to what is widely believed, 11-deoxycorticosterone is not devoid of 'gluco-corticoid' activity in *in vivo* tests. They have shown that when this compound is administered to adrenalectomized animals over longer periods than are usually employed in such tests, the liver and muscle glycogen can be restored to normal levels. It should be pointed out, however, that this finding does not necessarily conflict with the view that 11-deoxycorticosterone is itself devoid of 'gluco-corticoid' activity. It has recently been shown by Hechter *et al.* (1949, 1950; see also Pincus, 1949) that certain steroids become hydroxylated at C 11 on perfusion through isolated beef adrenal glands, and in this way they were able to effect the conversion of 11-deoxycorticosterone into corticosterone in high yield. It is conceivable that 11-hydroxylation might occur to a limited extent elsewhere than in the adrenal gland itself, in which event the 'gluco-corticoid' activity of 11-deoxycorticosterone in long-term experiments might be due to partial conversion into corticosterone.

Thirdly, recent work from several laboratories indicates that the 'mineralo-corticoid' 11-deoxycorticosterone may be as potent as, or even more potent than, certain of the 'gluco-corticoids' in affecting the carbohydrate metabolism of tissue preparations *in vitro*. Verzár and his co-workers (Leupin and Verzár, 1950), in experiments on isolated rat diaphragm, have shown that 11-deoxycorticosterone is somewhat more active than corticosterone, 17-hydroxycorticosterone and cortisone in inhibiting glycogen formation from glucose. In similar experiments on rat diaphragm, Bartlett and his co-workers (1949) have confirmed that 11-deoxycorticosterone is more active than corticosterone; whilst Chiu (1950) has shown that 11-deoxycorticosterone is as active as 11-dehydrocorticosterone in promoting

carbohydrate synthesis *in vitro* in rat and rabbit liver slices. These results obviously cannot be explained by supposing that a conversion of 11-deoxycorticosterone to corticosterone can occur elsewhere than in the adrenal gland.

The findings discussed in the foregoing three paragraphs would suggest that there may be no clear-cut distinction between the intrinsic biochemical activities of the 11-deoxy compounds on the one hand and the 11-hydroxy and 11-keto compounds on the other. It is possible that the observed differences in tests on living animals may to some extent be due to differences in the rates of absorption and excretion, and also perhaps to differences in the rates of metabolism in the tissues. Another point which should be borne in mind in this connexion is that the term 'gluco-corticoid' may in itself represent an over-simplification. As used by Selye, the term carries the dangerous implication that a single effect upon one type of biochemical reaction only is involved in the manifestation of 'gluco-corticoid activity'. It seems unlikely, however, that 'gluco-corticoid activity' can be as simple as this. In any test on a living animal for such activity the effect actually measured, e.g. elevation of liver glycogen, inhibition of the hypoglycæmic action of insulin, or production of glycosuria, must be the result of the effects upon gluconeogenesis from protein, upon glycogen synthesis and breakdown in the liver and other tissues, probably upon carbohydrate oxidation, and also possibly upon fat metabolism. There is no reason to assume that similar chemical mechanisms are involved in these different effects.

The outstandingly important work of Hechter, Pincus *et al.*, previously referred to, adds considerably to the plausibility of Selye's view that an 'unfavourable gluco-corticoid/mineralo-corticoid balance' in the adrenocortical secretion may be an etiological factor in the rheumatic diseases. There is nothing improbable in the idea that during hyperactivity in response to stress the enzyme system in the adrenal glands which effects the 11-hydroxylation of the 11-deoxy steroids might become overloaded, with the consequent release of the latter into the blood stream in excessive amounts. However, attractive though this idea is, it is not on the whole supported by the little evidence available at the present time.

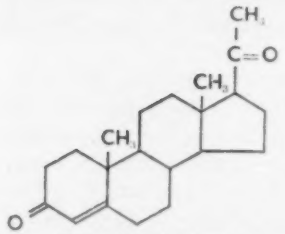
There is no direct evidence that any 11-deoxy-adrenocortical steroid, or any steroid with a predominantly 'mineralo-corticoid' action, is actually secreted by the adrenal cortex. Cortisone and 17-hydroxycorticosterone have both been isolated from human urine (Mason and Sprague, 1948; Mason, 1950; Schneider, 1950), and it can therefore be assumed that both are secreted by the gland. On the other hand, the other four active compounds have so far only been isolated from the gland itself, and it is therefore possible that they are present as precursors of 17-hydroxycorticosterone and cortisone and are not actually secreted. However, too much weight should not be attached to this purely negative evidence, in view of the very great technical difficulties involved in the isolation of the adrenocortical steroids in small amounts from natural sources. Furthermore, the possibility must

be kept in mind that the other four active compounds may be secreted by the gland but may be more completely metabolized to other products before reaching the urine than are 17-hydroxycorticosterone and cortisone. In this connexion it should be mentioned that pregnane-3α-17α-20α-triol, which is present in the urine of some cases of adrenal hyperplasia, might arise by the metabolic reduction of 11-deoxy-17-hydroxycorticosterone, whilst pregnane-3α:20α-diol, which is present in increased amounts in the urine of such cases, might arise in part from 11-deoxycorticosterone (see pp. 49-51). The possibility that the two 11-deoxy steroids may be secreted by the adrenal cortex cannot therefore be excluded.

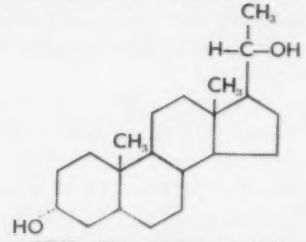
Perhaps the strongest evidence against Selye's views is that the rheumatic diseases in man are not normally accompanied by any marked disturbances in electrolyte metabolism. If excessive 'mineralo-corticoid' secretion were an important etiological factor, one would expect sodium and chloride retention and raised potassium excretion to be associated with these diseases.

PROGESTERONE METABOLISM IN RHEUMATOID ARTHRITIS

Findings.—It has recently been shown by Sommerville, Marrian, Duthie and Sinclair (1950) at Edinburgh that the metabolism of progesterone



VII.—Progesterone



VIII.—Pregnane-3α:20α-diol (pregnanediol)

(VII) administered to rheumatoid arthritic subjects, as judged by the urinary excretion of its principal known metabolite, pregnane-3α:20α-diol (VIII), is markedly abnormal. The significance of this finding is obscure at the present time, but the authors have cautiously suggested that it might be compatible with the hypothesis that rheumatoid arthritis is associated with an analogous abnormality in the metabolism of the endogenous adrenocortical hormones.

The work carried out in Edinburgh on the metabolism of progesterone administered to rheumatoid arthritic subjects was initiated soon after, and in consequence of, the announcement by Hench *et al.* (1949a,b) of the effects of cortisone in this condition. Initially two facts led us to consider as a tentative working hypothesis the possibility that rheumatoid arthritis might be associated with an abnormality in the metabolism of cortisone in the affected tissues, resulting in an increased local demand, rather than with a deficient secretion of the adrenocortical hormones. First, rheumatoid

arthritis is seldom associated with any of the well-recognized symptoms of adrenocortical insufficiency; and secondly, the minimum daily dose of cortisone required to induce a remission of the arthritic symptoms (100 mg.) is very much greater than the daily dose of 10 to 20 mg. which Thorn and Bayles (1949) have stated is sufficient to maintain Addisonian patients with complete adrenal insufficiency.

The possibility was next considered that if rheumatoid arthritis is indeed associated with some abnormality in the metabolism of endogenous cortisone, this abnormality might well be accompanied by analogous abnormalities in the metabolism of other closely related steroid hormones. This consideration finally led to the decision to undertake a quantitative study of the metabolism in rheumatoid arthritic patients of the corpus luteum hormone, progesterone.

Progesterone dissolved in oil was administered by intramuscular injection in a single dose of 60 mg. or in two doses of 60 mg. on successive days to normal and rheumatoid arthritic men and post-menopausal women. (Men and post-menopausal women were selected as experimental subjects in order to avoid any complications arising from endogenous progesterone.) The pregnanediol excreted subsequently in the urine was quantitatively determined. The results of these experiments shown in the table below include figures previously published (Sommerville and Marrian, 1950; Sommerville, Marrian, Duthie and Sinclair, 1950), and a number hitherto unpublished.

TABLE

URINARY PREGNANEDIOL EXCRETION IN NORMAL AND RHEUMATOID ARTHRITIC MEN AND POST-MENOPAUSAL WOMEN

Subjects	No. cases studied	Progesterone excreted as pregnanediol. Average percentage
Men		
Normal	8	11.1 (9.3-14.7)
Rheumatoid arthritic	10	25.5 (19.9-37.3)
Post-menopausal women		
Normal	10	14.4 (12.1-16.0)
Rheumatoid arthritic	15	25.5 (16.2-36.5)

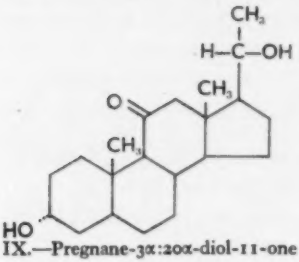
These results appear to admit of no other conclusion than that rheumatoid arthritics excrete as urinary pregnanediol an abnormally high proportion of progesterone administered by intramuscular injection.

It has been pointed out by Sommerville, Marrian, Duthie and Sinclair (1950) that the importance of the finding of this abnormality in the metabolism of administered progesterone in rheumatoid arthritis must remain in doubt until progesterone metabolism tests have been carried out in a wide variety of different clinical conditions, since it was clearly appreciated that this abnormality might not be specific to the disease. In an attempt to investigate this point, Sommerville (1950) has recently carried out progesterone metabolism tests on a few patients suffering from diseases in which there

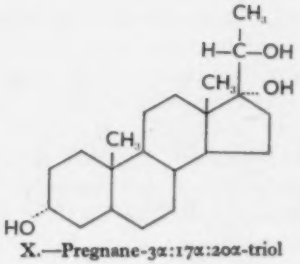
are certain clinical features similar to those found in rheumatoid arthritis.

In a single case of gout, the urinary pregnanediol excretion was found to be abnormally high. In four cases of spondylitis ankylopoietica, one gave a high pregnanediol recovery whilst the other three were within the normal range; in single cases of osteoarthritis, tuberculosis of the spine, and carditis following rheumatic fever, the pregnanediol recoveries were normal.

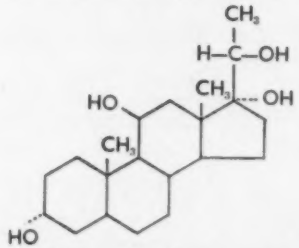
These preliminary findings suggest that the abnormality in progesterone metabolism may be quite limited in its distribution, and may not even extend to all of the other diseases which are said to respond to cortisone or ACTH therapy. Unfortunately, the total number of cases investigated in this work up to the present time is too small to permit of the drawing of any definite conclusions. Further work on the metabolism of administered progesterone in conditions other than rheumatoid arthritis must clearly be carried out as soon as circumstances permit.



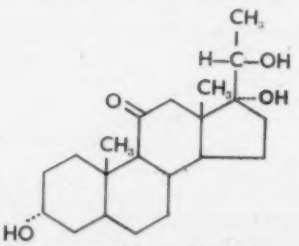
IX.—Pregnane-3α:20α-diol-11-one



X.—Pregnane-3α:17α:20α-triol



XI.—Pregnane-3α:11β:17α:20α-tetrol



XII.—Pregnane-3α:17α:20α-triol-11:one

Sommerville, Marrian, Duthie and Sinclair (Sommerville, 1950) have also carried out progesterone metabolism tests on a few rheumatoid arthritic subjects on the third day of a five-day course of treatment with ACTH, and although good clinical remissions were obtained, the abnormality in urinary pregnanediol excretion remained uncorrected in each case. This finding is compatible with the view that the metabolic error may be associated with the underlying cause of the disease rather than being merely a secondary effect of the arthritic condition. Until further tests have been carried out during more prolonged ACTH remissions, however, these results must be viewed with some suspicion and interpreted with caution.

Discussion.—It must be stated clearly at the outset of this discussion that

my colleagues and I do not claim that our finding of an abnormality in the metabolism of progesterone administered to subjects suffering from rheumatoid arthritis proves the correctness of the working hypothesis that the disease is associated with an analogous abnormality in the metabolism of the endogenous adrenocortical hormones. We still regard this hypothesis as a highly speculative one, but nevertheless one which has now been shown to be worth retaining as a basis for further investigations. Speculative though the hypothesis may be, the biochemical evidence which originally suggested it is worthy of critical consideration.

As shown by Cuyler, *et al.* (1940) and by Horwitt *et al.* (1944), 11-deoxycorticosterone acetate on administration to human subjects gives rise to pregnane-3α:20α-diol in the urine. More recently Mason (1948) has isolated pregnane-3α:20α-diol-11-one (IX) from the urine of two patients with Addison's disease after the administration of 11-dehydrocorticosterone. These findings provided clear proof that the body can reduce the C_3 and C_{20} ketone groups and the C_4 double bond in two of the active adrenocortical steroids in the same manner as it reduces the corresponding groups in progesterone.

Direct evidence for the occurrence of analogous metabolic reductions of the other four active adrenocortical steroids is not at present available, but the isolation by Butler and Marrian (1937, 1938), and Mason and Kepler (1945) of pregnane-3α:17α:20α-triol (X) from the urine of patients with adrenal hyperplasia, suggests the possibility that if 11-deoxy-17-hydroxycorticosterone is secreted by the human adrenal cortex (see p. 47), it may undergo the same process of metabolic reduction

By analogy with the above-mentioned instances, it is not unlikely that cortisone may undergo reduction in the body with the formation of pregnane 3α:11β-17α:20α-tetrol (XI) or of pregnane-3α:17α:20α-triol-11-one (XII). The fact that neither of these compounds has so far been isolated from human urine does not necessarily mean that they are not present, since it can be predicted that their physical and chemical properties would be such as to render their isolation somewhat difficult if the usual methods of extraction and fractionation were employed.

All the above-mentioned findings considered together provide strong support for the view that reduction of the C_3 and C_{20} ketone groups and of the C_4 double bond may be a general metabolic process with the C_{21} adrenocortical hormones. Since it is not unlikely that the same enzyme systems may be involved in these reductions as are involved in the reduction of the corresponding groups in progesterone, the tentative suggestion that an abnormality in the metabolism of administered progesterone may reflect analogous abnormalities in the metabolism of the endogenous adrenocortical hormones is at least plausible.

URINARY EXCRETION OF ENDOGENOUS ADRENOCORTICAL STEROIDS IN THE RHEUMATIC DISEASES

If rheumatoid arthritis and any of the related diseases are associated with or caused by any gross abnormality, either in the secretion or metabolism of the adrenocortical hormones, it might be expected that such conditions would be associated with qualitative or quantitative abnormalities in the urinary excretion of steroids of endogenous adrenocortical origin. It is important therefore to consider whether or not there is in fact any evidence for the existence of such abnormalities in any of these conditions.

The principal urinary steroids of adrenocortical origin may be broadly classified as follows:—

(1) *The C_{19} 17-ketosteroids.*—It is believed that in normal men about two-thirds of the total 17-ketosteroid excretion is due to the adrenal cortex and about one-third to the testis, whilst in women the adrenal cortex is the sole source of these compounds. Over twenty different 17-ketosteroids have been isolated from human urine (Dobriner and Lieberman, 1950), and it is possible that, to some extent, they may arise by the oxidative removal of the side chain of C_{21} 17-hydroxysteroids secreted by the adrenal cortex.

(2) *The C_{21} 21-hydroxy 'formaldehydrogenic' steroids.*—This group includes the active 'life-maintaining' or 'glucogenic' steroids in urine, such as cortisone and 17-hydroxycorticosterone, and perhaps other steroids possessing the same CH_2OH-CO- α-ketol side chain. Steroids possessing the CH_2OH-CHOH- α-glycol side chain, if present in urine, would be included in this group.

In view of the simple and accurate methods available for the quantitative determination of the total urinary excretion of the 17-ketosteroids it is surprising that comparatively few studies have been reported in the literature upon the excretion of these compounds in rheumatoid arthritis and related conditions. Davison, Koets and Kuzell (1947) have reported normal 17-ketosteroid values in a series of eleven women with rheumatoid arthritis, and values 'around the upper limit of normal' in thirteen men with spondylitis. More recently the same group (Report on International Congress on Rheumatology, 1949) has reported high 17-ketosteroid values in spondylitics of both sexes. Wolfson and associates (1949) have confirmed Davison *et al.* in finding normal values in rheumatoid arthritis (both sexes), but did not find elevated values in a small series of cases of spondylitis. Hench *et al.* (1949a) reported that the 17-ketosteroid excretions in rheumatoid arthritis 'were in low normal range', whilst Freeman *et al.* (1950) gave figures for the same condition which might be described in the same way.

These results, on the whole, provide little support for the view that rheumatoid arthritis or spondylitis is associated with any gross abnormality of the secretion or metabolism of the adrenocortical hormones. However, it must be borne in mind that an abnormality in the secretion or metabolism of the C_{21} 'life-maintaining' hormones would not necessarily result in any abnormality in the excretion of total 17-ketosteroids. Furthermore, it is possible that these conditions might be associated with a qualitative abnormality in the excretion of these steroids which would not be revealed by the methods employed. A more detailed study of the excretion of the different 17-ketosteroids in rheumatoid arthritis and other rheumatic diseases, like that recently carried out by Dobriner and his associates (1950) in cancer, might yield results of some interest.

Although perhaps outwith the scope of this article, the findings of Wolfson *et al.* (1949) that in gout the total 17-ketosteroid excretion is very greatly diminished must be briefly mentioned. This lowered 17-ketosteroid

excretion was not accompanied by any clear indications of hypogonadism in the male patients, and furthermore, was not accompanied by any decreased power of excreting 17-ketosteroids after the administration of testosterone. Accordingly, the authors have adopted the working hypothesis that in gout the adrenal cortex may secrete an abnormal androgen which makes no important contribution to the urinary 17-ketosteroids (see also Report on International Congress of Rheumatology, 1949).

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THE PATHOLOGY OF RHEUMATOID ARTHRITIS

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A CONSIDERATION of the morbid tissue changes in this disease raises many unsolved problems and, pending an answer to the question of etiology, any description of it must be regarded as tentative and inconclusive. Difficulty arises through lack of any precise definition of the disease and its relation to other clinically or pathologically similar conditions, and especially to other members of the group now known as the collagen diseases. For some, rheumatoid arthritis is the diagnosis restricted to the chronic progressive joint disease affecting primarily the hands of women. Others extend the definition to include cases with arthritis of the larger joints in both sexes in the absence of hand involvement. The episodic form of the disease with long symptom-free intervals is now a well-established conception, whilst rheumatoid disease without joint involvement is a theoretical possibility. Generally speaking, in late years the term has become more and more inclusive, and it is customary to speak of 'post-traumatic', 'post-gonococcal' and even 'post-acute-rheumatic' rheumatoid arthritis. These terms serve to emphasize that etiologically the disease may be non-specific in so far as the immediate external cause or 'trigger mechanism' is concerned, and that its existence as a recognizable clinical entity may depend upon intrinsic factors. This view has received some support from recent endocrinological research.

The pathological findings are in accordance with these rather vague clinical concepts of the disease. Although the tissue changes have in themselves little specificity, their association in joints, subcutaneous tissues, heart, nerves, muscle and elsewhere are sufficiently constant to provide a fairly characteristic picture of the disease as a whole. An unusual feature is the histological pleomorphism of the rheumatoid process. For example, in joints the cell-aggregations associated with the names of Allison and Ghormley (1931) have been generally accepted as characteristic and of diagnostic significance. In subcutaneous nodules the necrotic areas surrounded by a 'palisade' of young fibroblasts have been widely regarded as the most typical feature of the tissue changes, and these two patterns have nothing in common from the histological point of view.

It is proposed to describe the morbid processes as they are found on the various sites of the disease, and to discuss, and if possible integrate, them into a connected whole.

ARTICULAR PATHOLOGY

The disease is primarily a synovitis, and in the early stages the synovial membrane is swollen as a result of congestion and œdema, and later by

fibrous tissue increase. The synovial lining cells proliferate, and often three or more layers are seen over the more loosely attached portions of the membrane. There is a great increase in the number and size of the villous processes until a florid, grape-like profusion of villi may fill the joint cavity. This is especially true of the knee joint but may occur in less degree elsewhere.

Zones of superficial degeneration and necrobiosis may be seen on the surface of the membrane, sometimes involving a whole villus. The necrotic tissue is shed off into the joint cavity, where it may be found in advanced cases as yellow pultaceous material. A further evidence of necrotic change is seen within the thickened membrane in advanced cases. It is a fibrinoid focus surrounded by a palisade layer of mesenchymal cells, giving a lesion which is indistinguishable from that of the subcutaneous nodule. I have found this important link between articular and extra-articular pathology of the disease twice in membranes from the metacarpo-phalangeal joints in typical rheumatoid arthritis of women.

Cellular reaction takes the form of chronic round-cell infiltration. In the ligaments and capsule, the subsynovial fat and the deeper layers of the membrane, scattered paravascular lymphocytic accumulations are found associated, in the œdematous connective tissue, with a diffuse infiltration of lymphocytes, plasma cells and occasional polymorphonuclear neutrophils and eosinophils. Mast cells are also present in considerable numbers (Pearson, 1950). The most characteristic cell reaction, however, is seen in the villi, where large accumulations of lymphocytes and plasma cells form the so-called Allison-Ghormley foci. These consist typically of a central zone of loose texture containing large cells of endothelial type, surrounded by a dense mass of lymphocytes and plasma cells.

Associated with the active proliferation of synovial lining cells and villus formation there is often an effusion into the joint. This is not only an increase of normal synovial fluid, but is a true inflammatory exudate. As compared with normal fluid it is of lower viscosity and mucin content and contains protein derived from blood plasma, the fibrinogen present giving rise to slow clot formation. Soluble constituents, such as urea, uric acid and chlorides, are in the same concentration as those of blood plasma. Sugar is lower, probably due to utilization by leucocytes.

The cell exudate surprisingly contains a high polymorph proportion in a total count which is rarely less than 5000, and may reach 50,000, per c.mm. Such cell counts render the fluid turbid, but not frankly purulent as in suppurative arthritis. The abundant polymorphonuclear leucocytes in the fluid are in contrast to the paucity of these cells in the synovial tissues. They may represent a reaction to the superficial degeneration and necrosis already mentioned. In necrobiotic foci in the subcutaneous tissues and elsewhere polymorphs may be seen in the damaged tissues.

Culture of fluid for bacteria has given consistently negative results in the hands of all recent investigators. The consensus of opinion is that living

bacteria play no part in the perpetuation of the rheumatoid process, although infection as an initiating factor cannot be excluded. The work of Collins and Goldie (1940) on *Erysipelothrix rhusiopathiæ* infection of swine has shown that an initial infection may die out leaving a progressive chronic arthritis with many of the features of rheumatoid arthritis in man. If a comparable sequence of events occurs in human disease, bacterial infection must be regarded as only one of a number of 'trigger factors' of diverse type.

The second form which synovial reaction takes is in the *production of a fibrous pannus*, which is the major factor in causing destruction of articular surfaces. It starts at the point of reflection of synovial membrane over the margin of cartilage. A vascular layer of granulation tissue creeps over the articular surface, destroying and replacing the cartilage as it advances. The pannus may be found as irregular broad bands traversing the articular surface in different directions, resulting in serpiginous ulceration with survival of irregular cartilaginous islands. Apposition of pannus over articular surfaces in contact leads to the production of fibrous adhesions and loculation of the joint cavity. Cartilaginous metaplasia, and even ossification, may occur in old-standing adhesions, although true bony ankylosis is in my experience much rarer than some of the earlier descriptions would suggest.

Changes in bone occur simultaneously with those in synovial membrane. The radiological appearances of osteoporosis, marginal erosions and cyst formation are explained by the pathological changes in the epiphyseal marrow. There is fibrosis accompanied by bone resorption near the affected areas. Round cell infiltration takes the form of compact lymphocytic accumulations of small size. Penetration of the subchondral plate by vascular granulation tissues from the epiphyseal marrow may occur, but the appearances usually suggest that penetration is in the other direction. A narrow band of fibrous tissue may be seen, arising from the synovial pannus, passing through cartilage and bone and fanning out in the marrow space.

Natural 'cure' of the disease would appear to result from the union of opposed pannus layers and obliteration of all specialized joint tissues. This is rarely achieved. Cases may be active for periods of forty years or more and still show histological evidence of a chronic inflammatory process. The chronicity of the disease is almost unique in pathology. The 'burnt out' case, frequently referred to, is uncommon in my experience. The disease may remit spontaneously at any stage, but the possibility of recurrence always exists.

EXTRA-ARTICULAR LESIONS

Rheumatoid tenosynovitis and bursitis may occur, commonly producing soft swellings in the neighbourhood of the wrist. These show a villous inflammatory process histologically indistinguishable from that of the joint.

SUBCUTANEOUS NODULES

As in acute rheumatism, subcutaneous nodules are a common feature of rheumatoid arthritis, occurring in some 20 to 30 per cent. of cases. They

indicate the generalized distribution of the disease. Their site is determined by trauma and they are frequent over the olecranon process and the subcutaneous border of the ulna. The use of the elbow by partially crippled patients for raising themselves is the reason why this site is common. Others are to be found in the regions of the hands and feet. They vary in size from about 2 mm. in diameter to a large lobulated mass which may attain a diameter of 3 to 4 cm. They appear first as a proliferation of low-grade fibrous tissue in the subcutaneous fat with an increase of capillary vessels surrounded by a light infiltration of lymphocytes. Enlargement occurs by increasing fibrosis in the centre while the vessels and lymphocytes remain at the periphery, where they form a capsular zone recognizable even in the largest nodules.

A focus of degeneration of the so-called fibrinoid type then occurs in the avascular fibrous centre. This is a characteristic lesion in both acute and chronic rheumatism, but it is not specifically rheumatic. The mucopolysaccharide jelly-like ground substance, the cement which binds together the white fibres of collagenous tissue, swells up and is replaced by a fibrin-rich exudate. The fibres in turn degenerate, swell up, and later undergo fragmentation and disintegration. Such degenerate fibres and ground substance retain fibrin stains which gives the name 'fibrinoid' to the process which goes on later to complete necrosis and liquefaction.

At the periphery of the necrotic area there is a palisade layer of undifferentiated connective tissue cells, radially aligned, from which reticulin fibrils pass into the central zone. Surrounding the palisade, dense avascular collagenous tissue constitutes the main mass of the nodule, whilst at the periphery there is a zone containing small blood vessels surrounded by a variable infiltration of lymphocytes. The more superficial nodules are continuous with the deeper layers of the dermis, whereas others are wholly subcutaneous.

Spread of necrosis occurs at the expense of the palisade layer, which continues to re-form at an increasing distance from the centre of the focus. When liquefaction and cavitation occur this layer acts as a lining with pseudo-synovial characters. One end-result of nodule formation is the appearance of a thin-walled adventitious bursa, only recognizable as a rheumatoid nodule by the presence in its wall of minute 'bays' of necrotic tissue invested by a palisade layer. Lipoid deposition and calcification may occur in a proportion of nodules. Unlike the acute rheumatic subcutaneous nodule which is largely exudative, the rheumatoid nodule rarely disappears spontaneously.

NERVE LESIONS

Freund *et al* (1942) described focal lesions in peripheral nerves which they regarded as a part of rheumatoid disease.

They occurred in the perineural and epineural connective tissues, and resembled the focal cellular accumulations seen in the synovial villi and capsule in this disease.

In its most differentiated form the nodule shows three zones: a central homogeneous area, which did not give the staining reactions of fibrin and contained few reticulin fibrils, was surrounded by a zone of large irregular shaped epithelioid cells, and this in turn by a peripheral zone containing numerous lymphocytes and plasma cells. The outer zone was sharply differentiated from the surrounding tissues. Many of the nerve nodules were simpler in structure and consisted merely of a collection of mingled lymphocytes and epithelioid cells in close proximity to a vessel.

The occurrence of such focal lesions in perineural connective tissue has been confirmed by others, and they may be regarded as one of the generalized manifestations of the disease. They are comparable to the lymphocytic foci in nerve in acute rheumatism described by Koeppen (1932). There is no evidence that they interrupt the nerve or are concerned in the production of muscular atrophy.

SKELETAL MUSCLES IN ARTHRITIS

Muscular wasting is invariable in rheumatoid arthritis, and the histology is that of atrophy and degeneration. The fibres vary in size, some being shrunken and others swollen. There is a loss of normal staining reaction and of striation, with fibrillation or vacuolation of fibres. Sarcolemma nuclei are more numerous than in normal muscle, and their size, shape, distribution and staining reactions are abnormal. Freund *et al.* (1945), pursuing their studies on nerve lesions, examined muscle sections to ascertain whether the terminal nerve fibrils and myoneural junctions were involved.

They then found that in a high proportion of muscles large and small chronic inflammatory foci were present, ranging in size from 20 lymphocytes to a lesion visible to the naked eye in the stained slide. The larger lesions consisted of lymphocytes and plasma cells with histiocytes and, inconstantly, neutrophil and eosinophil polymorphs. The nodules were usually in relation to a vessel and were found in both endomysial and perimysial connective tissue. All were compact and well defined.

Later work by others has confirmed that such lesions may be found in 45 to 75 per cent. of small biopsy samples of muscle taken without regard to the site of other manifestations of the rheumatoid condition. Their diagnostic significance is reduced or nullified by the finding of similar lesions in other diseases, such as myasthenia gravis, dermatomyositis, disseminated lupus erythematosus, scleroderma, and acute rheumatism.

Of even more significance is the finding by Clawson *et al.* (1947) that lesions qualitatively similar to those found in rheumatoid muscle could be found in specimens taken at necropsy of patients who had died from a great variety of non-rheumatic diseases, and even accident and trauma. Thus 4.2 per cent. of 450 deltoid specimens were positive: intercostals and diaphragm gave the highest figures of 8 and 13.5 per cent., respectively.

In comparing these results with those of the various rheumatic series published, it should be noted that the size of samples from the cadaver can be much larger than those taken from patients, and that the two sites with the highest incidence of foci are not available for biopsy. Having recently examined a series of 365 muscles from 50 random consecutive necropsies in a general hospital, I agree with Clawson's findings. The lymphorrhages are not specific for rheumatism, but there can be no inherent specificity in a

collection of lymphocytes which is the almost universal accompaniment of chronic inflammation, of whatever cause, in connective tissues. Their interest appears to be in the now well-established fact that they are quantitatively much more numerous in rheumatism than in other diseases. At whatever point the rheumatic diseases are approached by the histologist, quantitative considerations in relation to non-specific reactions arise.

The tendons as a site of rheumatoid disease have recently been brought into prominence by a review of previous Scandinavian work, with important new clinical and pathological studies, by Kellgren and Ball (1950). The histology of rheumatoid changes is reproduced in this situation as elsewhere, modified by the pre-existing tendon structure.

THE HEART

Until the last decade the high incidence of carditis in acute rheumatism and its presumed absence in rheumatoid arthritis was regarded as a salient point of difference between the two conditions. Pericarditis was a recognized manifestation of juvenile rheumatoid arthritis (Still's disease), but clinical evidence of heart involvement was lacking in the vast majority of adult cases. Of late years, however, necropsy studies by a number of independent observers have shown an incidence of heart disease which ranged from 22 to 66 per cent. of cases. Endocardium, myocardium and pericardium have all shown a number of pathological changes with resemblances to those seen in the rheumatic family of diseases, but not all rheumatoid in type.

Thus Baggenstoss and Rosenberg (1941) reported mitral and aortic valvulitis, diffuse interstitial myocarditis with occasional focal lesions resembling Aschoff nodules, and fibrous pericarditis of subacute or chronic type. The lesions were not so severe or widespread as in the hearts of young rheumatic fever cases, but they regarded the differences as of degree rather than of kind. In a small minority of cases a more definitely rheumatoid type of lesion was seen (Baggenstoss and Rosenberg, 1944). Aortic and mitral valves and pericardium showed nodular foci with central necrosis and surrounding palisade, identical with that seen in the subcutaneous nodule. They described liquefaction and cyst formation in pericardial nodules.

From these and other studies it seems to be beyond doubt that the heart is not infrequently involved in rheumatoid arthritis, and that the lesions in a majority of cases had close affinities with those of acute rheumatism, but that in an important minority they reproduced the rheumatoid pattern of reaction. It is a subject for further observation to determine whether the arterial lesions which are seen, although infrequently, in rheumatoid arthritis are not part of a general cardiovascular involvement. Endarteritis of the verrucose type, medial degeneration and perivascular lesions, which might be interpreted as arising from the adventitial coat, are encountered which may parallel the changes described in the three layers of the heart wall.

THE BLOOD

The important findings are secondary anæmia, which is of hypochromic type, and an abnormal plasma protein constitution. The latter consists in an

increase of fibrinogen and of gamma-globulin at the expense of albumin, resulting in a reversed albumin-globulin ratio. The plasma protein abnormalities are the basis of tests used for assessing activity in the disease. These include the blood sedimentation rate estimation, plasma viscosity, and a group of tests which depend upon the colloidal lability of plasma or serum, such as the formol-gel reaction, Weltmann thermocoagulation test, serum colloidal gold and thymol turbidity tests. The significance of the plasma protein abnormalities is not clear. It is the experience of all who have studied the blood in this disease that cases with the most marked anæmia are those which show the most striking plasma protein changes. That the two phenomena are interrelated is further suggested by the dramatic return of both to normal after treatment with cortisone.

The leucocyte picture shows a moderate neutrophil increase in the early stages, but later it is surprisingly normal in the presence of widespread and active pathological processes in the joints and elsewhere. Neutropenia is extremely rare: Collins (1949) gives its incidence as less than 0.5 per cent.

DISCUSSION

From a consideration of the pathological changes described, it will be seen that the rheumatoid process is a general systemic one involving mesenchymal connective tissues in many parts of the body. The three cardinal features are:—

(1) Granulation tissue production, leading to overgrowth of fibrous tissue and destruction of the more specialized functional tissues.

(2) Necrosis beginning with the characteristic, but not specific, fibrinoid degeneration and passing on in certain instances to liquefaction and cavitation.

(3) Round cell infiltration of chronic inflammatory type. Lymphocytes predominate but plasma cells, histiocytes and polymorphs are also found in variable numbers. The result is a granulomatous lesion, the emphasis on each of the three components mentioned varying in the different sites of the disease. Thus in the joints, the pannus and Allison-Ghormley foci are predominant, representing the first and third components, but necrosis may always be found if adequate search is made, and in old-standing cases it may reproduce the form seen in the subcutaneous nodule. The latter is characterized by fibrosis and necrosis, but round cell reaction can always be found perivascularly in the capsular zone. The muscle and nerve lesions represent a predominance of the third feature. I have, however, noted fibrous scars in muscle, and in one case at necropsy a necrotic area surrounded by dense fibrous tissue was seen in the intercostal muscle. The recent detailed study of tendon lesions by Kellgren and Ball (1950) fits perfectly into this unified pattern of rheumatoid pathology. Variations within the single pattern are a function of the reactive capabilities of the different sites of the disease and of the phase at which the histological examination is made.

The important question of the specificity of these lesions is unsettled.

From the point of view of the general morbid histologist the changes are simply those of chronic inflammation in connective tissues. This question is sharply raised in connexion with the finding of lymphocytic foci in rheumatoid muscle, and by the demonstration of similar foci in muscles from normal persons and cases of non-rheumatic disease, although in a smaller proportion of cases and of specimens from each case. If the rather rare examples of true fibronecrotic lesions are excluded, it may be accepted that the difference in the incidence of lymphocytic lesions between rheumatic and non-rheumatic muscle is a quantitative one. Far from nullifying the significance of the rheumatoid findings, this fact must be fitted into the mosaic of evidence bearing on the etiology of the disease. Lymphocytic foci, fibrosis and muscle-fibre degeneration are not features of the histology of normal muscle. Their presence must presuppose a micro-trauma, whether this be toxic, bacterial or mechanical in origin. The last named would include the stresses associated with work done by the muscle. Clawson *et al.* (1947) noted the highest evidence in the diaphragm and intercostals, which have no physiological rest during sleep. The localization of rheumatoid disease in muscle may therefore be analagous to post-traumatic arthritis or the appearances of nodules in skin at pressure points overlying bone. The especial impact of the disease on the joints may be explained by the fact that of all mesodermal connective tissues, those of the joint are most subject to physiological trauma, namely, the frictional stresses of movement. Is the progressive rheumatoid process a continuation of the reaction to injury in tissues predisposed by intrinsic factors, or is it a new lesion superimposed on the traumatic reaction as tuberculosis is on an injured bone? This question appears to be cardinal in the interpretation of the pathological findings. The views of Selye (1950) would identify intrinsic factors with the hormonal effects of the stress reaction. At present a great void of ignorance remains to be filled between the demonstrable rheumatoid granuloma and the fact that the process may be reversed by cortisone. Between these two fixed points the field of future research is defined.

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GENETIC AND ENDOCRINE ASPECTS OF GOUT

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THERE is rapidly increasing evidence that clinical gout occurs only in those persons predisposed by hereditary hyperuricæmia, and who also develop an endocrine disturbance characterized by an abnormal regulation of the 11-oxysteroids of the adrenal cortex. The purpose of this report is to review the most important of the recent contributions which have led to this present concept of the pathogenesis of gout, and to discuss the significance of these studies in the practical management of patients with the disease.

HEREDITY AND GOUT

For many centuries it has been recognized that gout is probably a hereditary disease. It has been stated by many observers that in from 50 to 60 per cent. of all cases of gout there is a history of the disease in the parents or grandparents. In most of these reports the figures were based upon the patient's statements, and no attempt was made to verify the diagnosis by examining the relatives. Therefore these early reports are valuable only in that they suggest the hereditary tendency of the disease; they do not permit an accurate analysis, nor do they indicate the mode of transference of the hereditary tendency.

Garrod (1859) was the first to suggest that gout would probably be found to be due to a dominant Mendelian factor which expresses itself fairly regularly in hyperuricæmia, but only occasionally in gouty arthritis. In 1913, shortly after the development of quantitative methods for determining blood uric acid, Folin and Lyman (1913) reported hyperuricæmia in a man 'in whose family there had been more or less gout'. Jacobson (1938) studied a son of each of two men with clinical gout, and a brother of a third patient; all of these individuals had elevated serum urate values. The first extensive investigation along these lines was by Talbott (1940) who studied 136 non-gouty relatives of 27 patients with gout, and found that 34 of these relatives (25 per cent.) had serum uric acid levels which were abnormally high. Unfortunately, the exact relationship of the persons with the elevated levels to the patients was not included in the report.

Recently, two reports based upon modern methods of genetic investigation have presented evidence which established with considerable certainty the exact pattern of inheritance in this ancient disease. These systematic investigations have included determinations of the serum uric acid values in the immediate members of gouty families, and indicate that hyperuricæmia without arthritis is indeed a common finding. Data from these two carefully controlled statistical studies show that inherited hyperuricæmia in gouty families is due to a single, dominant autosomal (i.e., not sex-linked) gene.

The first of these reports was by Smyth, Cotterman and Freyberg (1948).

They collected extensive data from 89 relatives of 19 gouty male patients and made a genetic analysis based upon these facts. The results showed that hyperuricæmia in these families was apparently due to a single, dominant autosomal gene. Another significant observation in this study was the confirmation of earlier reports of a higher average normal plasma urate concentration in males than in females. Recognition of this sex-difference was taken into account in classifying relatives into 'normal' or 'hyperuricæmic' groups. In this study, the mean difference for the two sexes was 1 mg. per cent.; the critical levels were 6 mg. per cent. in males, and 5 mg. per cent. in females. That age is another significant factor affecting the serum urate was clearly shown in this same report. In young children no difference in blood uric acid levels was found between males and females; in older children, however, higher uric acid levels were found in the males. These investigators offer the following explanation for the greater incidence of clinical gout in males than in females: this disease tends to develop in those persons of either sex whose mean uric acid levels exceed a certain value for a certain period, and since hyperuricæmic males tend to have higher absolute values than hyperuricæmic females, more males than females have gout.

The second report is the excellent genetic study by Stecher, Hersh and Solomon (1949). This study was made during the same time, and using similar methods to those of Smyth, Cotterman and Freyberg, but without either group being aware that comparable investigations were being conducted. It included biochemical data from 44 gouty families. Each group analysed their data by different methods, but the results of both studies were strikingly similar.

The present status of the genetic factors in gout and hyperuricæmia may be summarized as follows:—

(1) Asymptomatic hyperuricæmia is a frequent finding in the relatives of patients with gout. A single, dominant autosomal gene is probably responsible for the transmission.

(2) Gouty arthritis may develop in an individual of either sex who possesses sufficiently elevated serum urate level for sufficient time, this being less probable in the female, due to a lower normal level in women and to a lesser effect (i.e., lower penetrance) of the pathologic gene in this sex.

EVIDENCES OF ENDOCRINE DYSFUNCTION IN GOUT

During these hereditary studies, certain facts were established to indicate that the clinical manifestations of gout are related in some way to pituitary-adrenal and/or gonadal function. These facts may be summarized as follows:—

(1) The average normal plasma urate concentration in males is higher by approximately 1 mg. per cent. than in females.

(2) This difference in plasma urate concentration is also present in gouty patients and their relatives. Thus, in males who inherit asymptomatic

hyperuricæmia, the average plasma urate level is higher than that in females who inherit this gene.

(3) Males who inherit asymptomatic hyperuricæmia do not, as a rule, develop abnormally elevated plasma urate levels until after puberty. Female carriers of genetic hyperuricæmia do not usually develop abnormally elevated plasma urate levels until just before or after the menopause.

Further evidence to support the concept that the altered urate metabolism and the pathological physiology in gout are associated with pituitary and adrenal glandular function followed the introduction of ACTH and cortisone. Soon after ACTH became available in adequate quantities for use in human beings, Hellman (1949) reported the production of attacks of acute gouty arthritis in gouty patients in a symptom-free period by the administration and withdrawal of this hormone. Furthermore, this same report included evidence that the administration of ACTH during an attack of acute gouty arthritis caused a complete remission of the symptoms in a matter of hours. The administration of cortisone has also been shown to produce prompt subsidence of objective and subjective manifestations (Boland, 1950). The demonstration therefore that attacks of acute gouty arthritis can be precipitated and aborted by these hormones leaves little doubt that the so-called pituitary-adrenal axis plays a central part in the causal mechanism of gout.

Effect of ACTH and cortisone upon urate metabolism.—The next link in the chain of evidence that the metabolic defects in gout are directly related to the adrenocortical steroids was the demonstration that alterations in uric acid metabolism regularly occur with the use of either ACTH or cortisone. Thorn (1947) was the first to inject ACTH into human beings, and he observed that an increased excretion of uric acid in the urine was a consistent physiological response of stimulating the adrenal gland. Other studies soon followed (Hellman, 1949; Robinson *et al.*, 1948; Wolfson, 1950; Sprague *et al.*, 1950), and there is now abundant evidence that ACTH and cortisone administered to gouty subjects cause a transitory increase in uric acid excretion and a fall in the serum uric acid. This regulation is due, according to Wolfson (1950), to the opposing influence of the 11-oxysteroids (compounds F, E and A) and of androgens. In the individual with gout, he considers that an abnormal androgen of adrenocortical origin is active in urate metabolism. This interesting hypothesis has not as yet been confirmed.

Exactly how ACTH and cortisone cause increased uric acid excretion remains unexplained; the best evidence (Benedict *et al.*, 1950) based upon experiments in which isotopic uric acid was injected intravenously into gouty subjects, indicates that the uricosuria arises exclusively from an increased renal clearance of uric acid.

17-Ketosteroid excretion in gout.—Still further facts which bear on the endocrine aspects of gout have recently been presented. Wolfson and his associates (1949) observed that the urinary output of 17-ketosteroids was

uniformly greatly diminished in gouty patients, both during acute attacks and during asymptomatic intervals. Such decreases were not found in patients with non-gouty hyperuricæmia. Robinson *et al.* (1949) confirmed these observations in both male and female gouty patients. Being unable to explain the very low 17-ketosteroid output by other means, Wolfson proposed that biologic androgen activity in gout is maintained by an abnormal male sex hormone which, when metabolized, contributes only slightly to urinary 17-ketosteroid excretion. This 'gouty androgen' appears to originate in the adrenal cortex.

CLINICAL USE OF ACTH AND CORTISONE IN GOUT

Acute attacks.—As previously noted, Hellman (1949) was the first to report the dramatic and prompt control of the local manifestations of acute gout with ACTH. Since then numerous reports of the amelioration of gouty symptoms with this hormone have been published. An analysis of these reported cases indicates that in the majority of cases a rapid and satisfactory response of the pain, swelling, intense tenderness and temperature occurs within twenty-four to forty-eight hours. The onset of improvement has, in many instances, been noted to follow within twelve hours of the administration of 50 mg. of ACTH; in other cases, complete relief of the local gouty symptoms is noted in only six hours, with improvement beginning within one or two hours. At present, the most satisfactory treatment of an acute gouty attack consists in the administration of 50 mg. of ACTH intramuscularly every six hours; usually, no more than two or three doses are required. In general, ACTH has definite advantages over colchicine, giving satisfactory response in cases refractory to full doses of colchicine. The converse has been observed, i.e., unsatisfactory response to ACTH and complete relief with colchicine. One group of observers (Gutman and Yü, 1950) is not convinced that the response to ACTH is superior to colchicine. More clinical experience on this point is desirable.

Similar control of the objective and subjective manifestations of acute attacks of gout is produced by the administration of cortisone (Boland, 1950). Because large doses (200 to 300 mg.) of cortisone are required, and the onset of improvement is delayed, ACTH is considered the drug of choice.

Exacerbation of symptoms occurs in some cases following the discontinuance of hormone therapy. Of the seven cases reported by Gutman and Yü (1950) in which clinical response was virtually complete, this rebound exacerbation of symptoms occurred in all but two cases. In general, these exacerbations were mild, but constituted one major objection to using ACTH in the management of these patients. To prevent these flare-ups which follow the withdrawal of ACTH, Wolfson (1950) has recommended the concurrent administration of colchicine. In his experience, colchicine given during, or immediately after, treatment with ACTH effectively overcomes

the tendency of ACTH withdrawal to precipitate a renewal of the attack.

The schedule recommended is as follows:—

(1) Colchicine and ACTH are begun simultaneously and given at six-hour intervals until 75 per cent. to 95 per cent. improvement is attained. The dose of ACTH is 50 mg. given intramuscularly, and colchicine, 1/100 grain (0.65 mg.) given by mouth.

(2) When 75 per cent. to 90 per cent. improvement has been obtained, continue to give colchicine, 1/100 grain (0.65 mg.) orally, five times per day until the patient develops diarrhœa.

(3) At this time, discontinue the colchicine for twenty-four hours and treat the diarrhœa, if necessary, with paregoric and bismuth preparations.

(4) After twenty-four hours, resume colchicine, 1/100 grain (0.65 mg.) three times per day, and reduce the interval to twice per day if gastro-intestinal symptoms again occur.

(5) When the maximum tolerated dose has been found, continue to give this ration for at least two weeks.

Interval gout.—If ACTH is administered to a patient with gout during an interval or quiescent period for three to four successive days, and then withdrawn, acute symptoms of gout will begin during the third or fourth post-injection day. Since Hellman (1949) first reported this interesting observation, other workers have produced acute joint symptoms which resemble the classic picture of gout.

The electrolyte and water excretion preceding and during these acute ACTH-induced bouts of arthritis has been shown to be identical with the so-called 'gout cycle' of spontaneous gout first described by Talbott and associates in 1935. These changes can be interpreted as reflecting cyclic changes in adrenal cortical activity with acute symptoms occurring during periods of decreased function. Events long recognized as capable of provoking acute attacks of gout, such as trauma, infection, operation, and chilling, undoubtedly act through their ability to affect pituitary adrenocortical activity.

The production of acute attacks by giving adrenocorticotrophic hormone during a symptom-free period does not always occur. For example, Hellman (1949), using 150 mg. in divided doses for four days, was successful in three out of five trials; acute gouty arthritis developed only once in eight cases reported by Gutman and Yü (1950).

The contrary actions of ACTH in the gouty person, that is, both terminating and eliciting acute gouty arthritis, have stimulated much interest regarding the mechanism involved. This phenomenon has been interpreted by Wolfson (1950) as indicating that the gouty individual in a quiescent period is unable to respond promptly to 11-oxysteroid lack produced by the ACTH withdrawal; during the attack, ACTH stimulates the adrenal cortex to increase 11-oxysteroid, which relieves the attack.

CONCLUSIONS

(1) Clinical gout occurs in those persons predisposed by hereditary hyperuricæmia.

(2) A single, dominant autosomal gene is probably responsible for this transmission.

(3) Recent reports clearly indicate that abnormal pituitary adrenocortical function is associated with the causal mechanism of gout. (a) Males have higher normal uric acid values than females, and this sex difference is usually not manifested until puberty in the male, and the menopause in the female. (b) Gouty persons have a low output of 17-ketosteroids in the urine. (c) The adrenocorticotrophic hormone (ACTH) of the pituitary, and cortisone are capable of both terminating and eliciting acute gouty arthritis.

(4) There is an impressive body of evidence to indicate that final answers to the mystery of the etiology of this ancient disease may be found in the already heavily burdened adrenal cortex.

(5) Adrenocorticotrophic hormone (ACTH) combined with colchicine is recommended in the treatment of acute attacks of gouty arthritis.

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A G.P. LOOKS AT THE RHEUMATISMS

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THE general practitioner who is so often told that he is in the front line of medicine and who is forcibly reminded of it from time to time by the inanities, or at any rate the eccentricities, of the 'brass hats', has to have some very definite ideas about that motley collection of the enemy, loosely called 'the rheumatisms'.

It is all very well for the pundits at the base to talk knowingly and familiarly of corticosteroids, to scoff at the old beliefs as did the report of the Empire Rheumatism Council on the etiology of rheumatoid arthritis last April, to say that allergy, psychological factors and focal sepsis are 'of doubtful or no etiological significance' because they haven't quite the courage to say 'little or nothing to do with', to conduct Gallup polls at a gallop; it is all very well for Dr. Collings (of the Southern Hemisphere) to urge G.P.'s to be more scientific and estimate their patients' sedimentation rates, but the fact is that the G.P.'s mind on this subject is moulded by the daily stories of being suddenly struck down, blurted out to him as though they were unique human experiences, and by the compulsions of pain, stiffness, fixity and humiliation in his patients. He has to have some system of thought in dealing with his rheumatic multitude, some embracing theory such as Leonard Williams loved and displayed in 'Minor Maladies', which may be unscientific, but is eminently workable. Selye's complicated 'adaptation theory' is not a handy tool in the G.P.'s bag. Generally the basis of this system, the *causa causans*, but acting remotely as the spirit of the Kremlin does in Communism, is sepsis.

Now this is what the Empire Rheumatism Council says about focal sepsis in rheumatoid arthritis:—

> At medical examination of 532 patients and controls, foci of infection were found in 22 and 10 per cent. respectively. The incidence is much lower than is usually reported in the literature on rheumatoid arthritis. The data on focal sepsis in this series were collected by a number of doctors whose views on what deviation from the normal should be accepted as pathological would differ greatly. Since no information is available on the length of time focal sepsis had been present or whether it preceded or followed the onset of rheumatoid arthritis, its significance as an etiological factor remains in doubt. Moreover, the small difference in incidence of 12 per cent. between patients and controls found in this investigation should be accepted with caution, since a recent investigation carried out in Edinburgh by an experienced otolaryngologist showed no significant difference between patients and controls in regard to the incidence of focal sepsis in the ear, nose and throat, or preceding upper respiratory infections.

As Mr. Churchill might say, 'Never in the history of Medicine has so amateurish a pronouncement been made on so important a question by such a learned body of men', two of whom may be quoted from their more individual moments. Sir Adolphe Abrahams wrote in Copeman's excellent

'Textbook of Rheumatic Diseases' (p. 382): '. . . there is abundant evidence to incriminate the causal relationship of sepsis in many acute and chronic rheumatic conditions and its aggravating influence in more'; and Professor L. S. P. Davidson on p. 122: 'The removal of septic foci produces a dramatic improvement only in a minority of cases [of rheumatoid arthritis]'. No one suggests that ordinary rheumatoid arthritis is the quick result of contemporary sepsis, but in a disease of obscure origin he who neglects clues like this must be obtuse indeed. L. Schmidt, indignant also at this Report, wrote (*Brit. med. J.*, May 20, 1950): 'I have yet to meet the experienced rheumatologist who has not witnessed almost daily a tonsillitis or sinusitis, followed closely by rheumatoid arthritis'.

After all what are the facts? The rheumatisms range from the transient arthritic responses to virus infections like influenza and to trivial illnesses, the arthritic responses to invasion by the gonococcus and a dozen other specific germs, metabolites and drugs, through rheumatic fever which is the response to invasion by a hæmolytic streptococcus or some jackal thereto, to rheumatoid arthritis which itself ranges from a response indistinguishable from rheumatic fever except in its results, to something very like osteoarthritis, then to the degenerative osteoarthritis, and finally, to the non-articular rheumatisms, lumbago, sciatica and the like, which rarely, but then dramatically, can be shown to be due to focal sepsis. But that it can be shown sometimes is vastly important, like tracing one industrial strike here straight to Moscow. The whole rheumatic octave is vibrant with sepsis.

How then came the thirty distinguished rheumatologists to sponsor the Report, which in the main is the statistical treatment of ambiguous questioning and unchecked answers and which in the matter of focal sepsis is misleading and, if taken seriously, would be mischievous; a truly pseudo-scientific production, the statistics being scientific, the material which they manipulate being pseudo? It is not the first time that the man in the front line has been amazed by the pronouncements of those at the base, but to the G.P. will come the comforting voice of William McDougall, who pointed out why the decisions of a body of men are so often unworthy of any one of them individually.

Although the G.P. regards sepsis or metabolite as the *fons et origo* of rheumatism he remembers that 'the demonstration of streptococci, gonococci, pneumococci, *Br. abortus*, *B. tuberculosis*, or other organism in joint fluid may be said to remove the case from the rheumatic group' (Copeman, p. 427). That is to say, the action is remote, the presence of the organism at the lesion (but not of the metabolite) disqualifies the holder from entering the rheumatic stakes; the rheumatisms are the joint, muscle and fibrous tissue responses to an invader, mediated by the body's defences. Here it may be that there will occur to the practitioner one of those long thoughts so characteristic of general practice: are not the rheumatisms and the like intermediate between frank invasions by organisms and saprophytic mateyness

with them? Before we go on to explain how the G.P. builds up his theory of sepsis, often of the mildest kind and scarcely perceptible, intermediated by the body's defences, the strong points of which are the hormonal glands, varying from a tough team to a scratch side, which before the menopause or an injury may have been a tough side too, we shall have to make two slightly annoyed incursions into the obvious for the benefit of the retreating Dr. Collings. Apparently he never realized that the principal instrument in general practice is the G.P.'s mind, with its mass of case law, its knowledge of local character and of the local prevalence and incidence of disease, with its almost instantaneous unverbalized reasoning, with its neat little hypotheses. Let us be simple and pedagogic, so that he can understand.

INCURSIONS INTO THE OBVIOUS

The Paul phenomenon.—An oculist once told me that when he started on his specialism, for about six months he felt that going round the fundus was a vexatious business as though he were finding his way in a maze. Suddenly, and he could remember the time and place—as on the Damascus road—there came to him enlightenment, and since then his eye has strolled round fundi as though they were his own garden. I had the same experience with chests: for months I had been examining many chests daily, trying to make the physical signs correspond with what they ought to be from the X-rays and textbooks, and *vice versa*, and being sadly puzzled by my inability to do so. Suddenly—and I can remember the patient I was examining thirty-five years ago—I felt quite at home on chests, relegating textbooks and X-rays to the witness box, while I assumed the ermine and stepped on to the bench. Subject to the Hallam phenomenon (see below), I have felt at home on chests ever since. I think that anyone who has acquired a skill goes through the same process, but it is not always so sudden.

Now all or most of those fifty G.P.'s with whom Dr. Collings 'sat in with' had experienced the Paul phenomenon in dealing with their patients' distresses, especially the indefinite ones like the rheumatisms. When a patient came into any of those surgeries where Dr. Collings scowled he benefited by the thousands of his like who'd come before and by the habit paths of thought in the doctor's mind. Dr. Collings saw a new case and heard a few perfunctory questions; the doctor saw one of a series, possibly going back half a century, and the questions were for the purpose of directing the matter to that part of his memory where many similar tales were stored.

The other exasperated simplicity I must inflict on the reader is the *Hallam phenomenon.* Hallam was a great dry-fly fisherman, who could cast an artificial fly, weighing a few grains, in a wind twenty yards across a river which, of course, flowed more rapidly in the middle than at the sides, with the line curved in such a way that when the fly floated over the exact spot where he had seen a fish rise the line was straight and did not drag on the fly and make it appear unnatural. *But*, at the beginning of the season or if

Hallam had been kept from fishing for any length of time, for the first two or three dozen casts he fumbled like a novice. Now Dr. Collings advises G.P.'s to do various laboratory procedures such as estimating their patients' sedimentation rates, and if the G.P. lives in the wilds this may be sound advice. The vast majority do not, and unless the G.P. is doing these laboratory procedures regularly he will experience the Hallam phenomenon each time and his results will not be accurate. I have done thousands of pneumothorax inductions and refills, but if I had to do one today I should be as nervous as a débutant. I have also done some 250 'locums' as against Dr. Collings' fifty 'sittings in with'. How often have I seen the dusty microscope and stains, the unused apparatus for estimating blood ureas, sugars, counts and whatnot! In answer to a question one generally gets, 'Oh, I used to be rather keen on . . ., but I gave it up. Not much time'. Actually it is not only the time that made them give it up, but the inaccuracy in one who is not dexterous by daily use in an affair where accuracy is the only essential. Estimation of the sedimentation rate (E.S.R.) is a most valuable indication of a patient's state, and a series of them, of his progress; it measures tissue destruction and exudation, probably because fibrinogen encourages rouleaux formation; it is not raised only in infective processes—'during acute attacks of gout the E.S.R. is much increased' (Copeman, p. 428); if done by an habitué it is a guide and friend; the G.P. must always remain the philosopher to interpret it.

So much for the sketchy E.R.C. Report and the callow Collings' Report: medicine is not the only sphere where the front-line worker is hindered by the naïveties of those in high places.

BACK TO BUSINESS

Having established therefore that the G.P. must have systems of thought, especially in dealing with the indefinites, having defined the rheumatisms as the remote articular or fibrous effects of invasions by toxin, metabolite or drug, having postulated that the body's defences are the mediators, especially the hormonal system, let us see how one system of thought was built up in the mind of one G.P.

Like most thought complexes it has its foundation in early impressions and is built up from an initial case, a schoolboy hero, a mighty athlete, who for some unknown reason had the distinction of defæcating only once a week. In my young mind this gave rise to a linking between physical prowess and constipation, and with them a certain lordliness, as of one who is above the common calls of humanity, an inability to enthuse or unbend, a dull judiciousness, which to hero-worshipping eyes made this young Achilles remotely Olympian. When years later my mind was trying to make some workable system of thought about the rheumatism problems that daily beset me, and I heard that this splendid physical specimen had developed an osteo-arthritis, the opportunist mind flashed back and made this one case the

foundation stone of a system, the four corners of which are costivity, athletic prowess, lack of emotion, arthritis.

Moderns scoff at the old notion of alimentary toxæmia in spite of the muddled heads of the occasionally costive, the putty faces of the habitually costive, the fresh complexions of colostomies, and the good example of natives (who have remarkably little rheumatic trouble) and of dogs in using the whip-end of peristalsis to void and make room at the top of the queue after every meal. No one dreams of denying that the gut is the largest absorbing surface in the body, or that in typhoid, which has a peculiar arthritis of its own, and a host of other enteric diseases, and in worm infestations, it lets through poisons that alter the character of man and child.

Besides, costivity harms not by toxæmia alone; speeding the departing guest whom one has robbed of his jewels and loaded with the things one does not want is an occasion for the rejoicing of the whole body, especially that differently gifted group, the hormonal glands. Consider for a moment the act of defæcation, not the flabby account as the textbooks give it, but as every brother and sister at stool knows it subconsciously, but not subconsciously enough not to enjoy it. And here let me interpolate that the prudishness that envelops the important subject of defæcation comes from the fact that for reasons of hygiene Nature makes us abhor the excreta of another (except a mother her child's), and also from the economies of divine wiring, the pudendal nerve being made to serve for sex and defæcation; nobody ever gets prudish about the small intestine or even the pelvic colon, so far as I know.

The rectum starts to grumble at the burden imposed from above; the parasympathetic and sympathetic, like rival solicitors who nevertheless work within a code, decide on mutual action; they put up a prayer to the Suprarenals: 'Oh Gods above the kidneys, help us move this mountain from our path'. The Suprarenals send a message to the Pituitary: 'About to aid Symps in moving mountain, please render all possible assistance'. In the Pituitary office the typewriters click and the couriers strain at the leash, one of whom is instantly sent to the Suprarenals. The Thyroid is warned as a routine in cases of emergency. A note is sent to the Testes and Ovaries: 'Mountain about to be moved in your vicinity stop please note this has priority over bladder stop render all possible . . .'. A dutiful note is sent to the Cerebral Cortex: 'Sire, may I be permitted to draw your attention . . .', which evokes a gracious reply: 'It is noted that We are about to defæcate. Please proceed We are busy on Matters of State'—probably reading the paper or knitting. And when it is all over with the Victory glide and roll there is great rejoicing, the wires hum with mutual congratulation. 'A great riddance, my brothers!'

Anyone who has watched a dog or a child after defæcating will have noted the joyous kick of the hind legs and scamper away or the sudden renewed interest in some triviality; a new cycle has started. It may be that here will occur another of those long thoughts so consoling to the G.P. on his daily round, especially if he has ever lived with a native people. Man's civilization consists very largely of obscuring the daily cyclothymias induced by eating and defæcation, by sleep and activity, as well as the monthly and seasonal cyclothymias.

In the case of my archtype, in the case of young Achilles, in the five thousand days of his boyhood he was largely deprived of this unplugging, this catharsis of the spirit, and who can doubt that this accounted for this solid commonsense unemotionalism, or that the energy which was thereby saved was used to build up a mighty man of valour, hormonal mouldings. Some developmental defect, some slight adhesion, perhaps some skin lesion with a deep reflex caused the costivity, the hormonal adaptation followed; the osteoarthritis was the result of that adaptation. How? I think like this: The hormonal defences were of necessity first withdrawn in part from those structures which have always had to compromise between having strength and having vascularity—the fibrous bands. Klinge described the basal lesion in rheumatism as fibrinoid degeneration or fibrinoid swelling. The highly vascular joint, the hinge which must have blood or cease to swing, is involved secondarily. It is quite easy to see how other constant threats, infected tooth sockets and tonsils and nasal sinuses or even skin lesions can act in the same way as costivity in Achilles: cause a hormonal moulding for their repression, thereby weakening the outposts of vascularity, robbing of movement that which needs blood most, the joint, and if prolonged, altering character. In each infected person—and who is not infected?—there must be a balance; the upset of the balance is rheumatism on the one hand, increased health and characterization on the other. That is why so much rheumatic trouble appears at the menopause, when the Pleiades of the hormonal glands reduce and change their brilliancies; the average age for the onset of rheumatoid in males and females is about forty and the fattening menopausal woman with the osteoarthritic knee is in every surgery; the early severe form of rheumatoid occurs in young females of asthenic, visceroptopic, narrow-chested type—in them with congenitally poor defences.

HORMONAL INFLUENCES

If then one looks at the rheumatisms as invasions by toxin, metabolite or drug, mediated and unsuccessfully mediated by the body's defences, and especially by those specialists, the endocrines, who are so specialized that they have a trade union rule that if one is consulted all must be consulted, the whole jigsaw begins to fit together. The transient stiffnesses after influenza and virus diseases or sitting in a draught are mere temporary defeats, soon made good; the average rheumatoid is the result of perhaps twenty years ding-dong battle, lost when the more virile defences weaken; Still's disease, in which the infection can often be traced, is a blitz and the hormonal humiliation is pitiable—I can see the hopeless expression of the first one I looked after thirty years ago; osteoarthritis is a local defeat, often of the most used joint, the toe of the ballet dancer, the elbow of the stoker, or of a joint, handicapped by old injury, generally after many years of fighting, which has left a hormonal moulding, a toughened character. The G.P.

will weigh this balance on his daily round, wonder at it, and formulate his treatment on it.

Browsing through Copeman's 'Textbook of Rheumatic Diseases' I have collected the following items to sustain the argument that the hormonal emphases are altered in the rheumatisms, and it must be remembered that one gland cannot be influenced without altering the others: as Francis Thompson might have sung:

> 'All things by immortal power
> Near or far,
> Hiddenly
> To each other linked are,
> Thou canst not stir a testicle
> Without troubling of a pancreas'.

(1) Freckles the most diagnostic point in the early diagnosis of osteoarthritis. Garrod thought this was true of rheumatoid arthritis (p. 16).

(2) Rheumatoid—'disease occurs in severe form in young females of asthenic, visceroptopic, narrow-chested type' (p. 121).

(3) Acromegaly associated with osteoarthritis.

(4) Monroe found osteoarthritic changes in a third of all his cases of myxœdema, of 1.6 per cent. in 414 cases of hyperthyroidism (p. 159).

(5) Close connexion of obesity and osteoarthritis.

(6) Also of osteoarthritis and hypertension, a large number of cases of which may be considered as suffering from the opposite of Addison's disease.

(7) Artificial menopause—a cause of rheumatoid- and osteo-arthritis.

(8) Enlargement of the thyroid in rheumatoid arthritis.

(9) Average onset of rheumatoid arthritis comes at about forty years of age.

(10) 'Osteoarthritis is said to attack the adipose, the thyroid-deficient, and the menopausal patient' (p. 166).

(11) A definite connexion between psoriasis and rheumatoid arthritis, both of which tend to disappear in pregnancy (p. 187).

(12) 'There are several diseases in which arthritis, arthropathy or arthalgia may occur as an incidental feature of the clinical picture . . .', the list includes hyperparathyroidism and myxœdema (p. 231).

(13) Hippocratic aphorisms quoted—eunuchs, women before the menopause, and lads before they take to copulation do not take the gout (p. 249).

(14) 'Minor degrees of osteoarthritis of the knee joint often occur at the climacteric in middle-aged women who have recently gained weight'.

(15) Finally, like a hesitant Q.E.D., there is cortisone and ACTH.

Obviously, if the hormonal glands are the moulded mediators between toxin or metabolite and the various lesions of rheumatism, the clinical pictures will tend to run into each other. Here is some evidence to sustain this proposition:

(1) Rheumatoid arthritis in a typical form (5 to 10 per cent.), onset abrupt with high fever, intense constitutional disturbance and widespread articular symptoms: 'This picture may mimic rheumatic fever so closely that it may be impossible to make an exact diagnosis until some weeks or months have elapsed', i.e., until the joints are clear or have stuck (p. 130).

(2) 'Gonorrhœal arthritis may have clinical features identical with those of classical rheumatoid arthritis, but . . .' (p. 131).

(3) 'According to Thomson and Gordon, practically all people who suffer from gout suffer from fibrositis' (p. 309).

(4) Rheumatic fever in older subjects: 'The differential diagnosis from acute rheumatoid arthritis may on occasion present considerable difficulty, especially as the development of cardiac lesions in rare instances provides reason to suppose that there is a close etiological association between the two conditions' (p. 381).

(5) Lumbagos, sciaticas, torticolles—'Such cases may be seen in their most classical form as a sequel of undulant fever' (p. 319).

(6) 'Unless the observer be a slave to names it must be allowed that it is not always easy to call a case one of rheumatoid arthritis or of osteoarthritis'. This sentence comes from the same Lord Horder as of the Report, but here he is singing a delightful duet with Copeman in the belly of the whale, Price (p. 1376).

A FEW CASE HISTORIES

The case of Achilles is invaluable because if such a magnificent specimen can get a degenerative arthritis then the broad lines of the mechanisms should be apparent, and, I think, are. I have often seen the character moulding in the person who only became a case at the menopause or after some other illness, but in whom a lifelong, ding-dong, almost unnoticed battle with sepsis had taken place.

A very bossy woman of forty got rheumatoid arthritis. Her friends said, 'Poor dear, that's a Nemesis on bossiness'. Really the bossiness was caused by a low-grade and long-standing sinus infection and was comparable to the courage and emotional clipping of Achilles, as a careful history-taking, followed by a relentless cross-examination, showed.

In the chapter of Copeman's book on 'Psychogenic Rheumatism' this sentence occurs on p. 562: 'Arthritis-like pains are in our experience relatively common (and often quite intractable) in strict Baptists, Salvationists, Plymouth Brethren etc.'. Generally these creeds or cages are inherited, but when they are not, when they are 'of etiological significance', to use the jargon of the Report, they too, are variants of the moulded character seen in Achilles.

I have space for only a few case reports. Here is a very common type of hoarding case:—

A solicitor who used to have protean attacks of fibrositis which he called 'my screws'. He was a dried-up, port-and-walnut, orthodox, C. of E., one-motion-a-day-at-8.55-a.m. sort of man. One day he said to me, 'You write, don't you? I have a very clever plot for a story. Promise me you won't use it?' I promised. 'Mind you, it is my property, I shall write it myself'. It was of the slick variety like O'Henry's. That was ten years ago and the story is not written yet. The bowel hoarding had given rise to a narrowed circle of cyclothymia, and the moral: Damn it all, you cannot receive if you do not give, you cannot take in if you do not cast away, a low bodily metabolism must run with a low spiritual metabolism.

Here is a case which shows cortisone in natural action:—

A doctor's wife who in spite of gross deformities of hands and feet ran her house, drove a car, and even hunted. The story was that the rheumatoid arthritis had come on in her thirties and for ten years she had been the querulent, waited-on type. Then her husband had lost all his money and she had staggered back to normal activity. 'Marvellous will-power! Heroic. The truth is her suprarenals had been stimulated by fear of disaster. Electro-convulsive therapy ought to be good for early rheumatoids.

The euphoria before gout probably corresponds with 'diuresis with in-

creased concentration of urinary solids, especially sodium and chloride, which precedes an attack of gout, probably a cyclical attempt at excretion which fails in its purpose if an attack follows, for it often occurs in gouty subjects without an attack following. Something very like it occurs in other forms of rheumatism and there is a definite *amor habendi* in the euphoria.

A cameo: I am at the bottom of the stairs just down from seeing a man with lumbago. His wife confronts me. 'Lumbago again!' she snorts. 'I don't wonder. He came home and mowed the lawn, then he sat in his damp clothes and went through his investment papers, then he went out and cut the hedge and came back and pored over his stamp collection. Then he is furious because he gets lumbago!'

The most interesting rheumatic case I have ever come across was while doing a 'locum' in Norfolk in 1938.

I had a patient, an elderly woman with rheumatoid arthritis of the don't-touch-the-bed type. She had had one kidney removed for stone, and during my tenancy the sole ureter was blocked by stone for three or four days, causing complete anuria. During this time she lost her pain, got back some movement and, what amazed me, expecting uræmia, became almost cheerful. After she had passed the stone the old symptoms returned. She lived until 1948 and this sequence, I am told, occurred about a dozen times.

The undoubted benefit in all the rheumatisms from swilling quantities of water, especially at a sitting, is due far more to the hormonal response which may be construed as 'By God, we're getting water-logged!' than to the elimination of toxins. One of the stages in the action of cortisone is fluid retention.

Compare the quick response in this last case to a sudden threat of death, to the gradual response throughout his boyhood to a minor threat in Achilles.

CONCLUSION

When I was writing this I thought I had better find out how my archtype was getting on, so I broke a twenty years' silence with a postcard and got a reply by return: 'I do the garden, but digging is a slow job and to lift the potatoes I have to be a contortionist . . . I still manage to referee in village soccer games'.

Dear old Achilles! What glorious 'guts'!

'WART, I BID THEE BEGONE'

By W. R. BETT, M.R.C.S., L.R.C.P., F.S.A.Scot.

WARTS are apt to be regarded as trivial by all except their possessor, and mankind's eagerness to be rid of them is reflected in the number and variety of 'cures' which have been advocated through the ages. These 'cures', incidentally, are not tried solely for cosmetic reasons, for some people believe that warts may give rise to cancer.

POPULAR THOUGHTS ON CAUSATION

Warts are often considered a sign of good fortune or of bad luck. The appearance of a wart on the right hand, for example, was believed to foretell sickness. There was, and still is, a widespread superstition that association with the lower animals, such as cows and fowls, is a cause of warts, whilst continual moistening and dirtying of the hands has been similarly blamed. Handling of the female genitalia has been mentioned as an etiological factor. One hundred and fifty years ago a doctor wrote that in his opinion the presence of warts on the fingers of unmarried women was a certain sign of masturbation. A note in the *Lancet*, 1849, **ii**, 250, tells of a girl 'accustomed to search for the near laying of eggs by introducing the index finger into the cloaca of hens'—she had many warts on that finger.

The idea that warts owe their origin to washing the hands in water in which eggs have been boiled still survives in the North, whilst in parts of Ulster the foam of the sea-shore is held responsible. To kill a toad is to invite a visitation of warts, according to a New England belief, their number being equivalent to the number of the toad's spots.

ARE WARTS CONTAGIOUS?

The lay belief that warts are infectious was scorned by the medical profession until 1894, when Gastron Variot, a Paris pædiatrician, confirmed its truth by inoculating warts from a child into an adult (*Journal de clinique et de thérapeutique infantiles*, 1894, **2**, 529). The credit for the first scientific observation on this problem should, however, go to Joseph Frank Payne, the great English medical historian and bibliophil. When he was physician to St. Thomas's Hospital, he contributed an article, 'On the Contagiousness of Common Warts', to the *British Journal of Dermatology* (1891, **3**, 185-8):—

> 'The widely spread popular belief that common warts are transmissible from one person to another, as well as from one part of the skin to another part, is generally treated by writers on dermatology either with silence or contempt . . . For myself, I have long been of the opinion that the popular belief is correct, though opportunities do not often occur for establishing the fact of contagion on definite evidence'.

He reports the case of a boy aged eleven years, with 'a very copious eruption of warts'. These were rendered soft and crumbling with salicylic acid-collodion and acetic acid, when they could be scraped away with the

back or handle of a scalpel. On one occasion the author 'thoughtlessly' used his thumb-nail to 'assist the operation'. The result, however, convinced him once for all of the contagiousness of warts, for a few days later he noticed some redness and swelling under the thumb-nail, and in about a week 'an unmistakable horny wart appeared on the spot', followed by two warts on the back of the thumb. In a few weeks these all disappeared spontaneously.

TRANSFERENCE

Many popular 'cures' for warts, some of which can be traced to the fourth century, owed their success to the alleged transference of these lesions to another person, an animal, a plant, or an inanimate object. One method consisted in rubbing the warts with a cinder, which was then tied up in paper and dropped 'where four roads meet'. The unfortunate individual who opened the packet would then be rewarded for his curiosity or greed by having the warts transferred to his body. Two other ways of unburdening oneself of these excrescences and of inflicting them on someone else were: to fill a bag with as many small pebbles as there were warts and to toss it over the left shoulder, and so to transfer the warts to the person who picked up the bag; to tie a string with as many knots as there were warts, to lay this under a stone, and thus to get rid of the warts on to anyone treading on the stone.

In Scotland, victims of warts lifted a stone at four cross-roads and rubbed their warts with the dust beneath it, repeating this rhyme:—

> 'A'm ane, the wart's twa,
> The first ane it comes by
> Tacks the wart awa'.'

The rationale of the following trick seems rather obscure to us today: rubbing the warts against a man who was the father of an illegitimate child—but without his knowledge—speedily removes them. Although transference of warts was usually attempted without the knowledge or consent of the intended victim, people would occasionally volunteer their help. In Cornwall vagrants would undertake the removal of warts by the following means: they would carefully count the number of warts, write them on the inside of their hat, and, leaving the neighbourhood, would take the warts with them.

Records of warts being transferred by sale are quite common. If the victim could persuade a charitable friend to buy his wart for a halfpenny, it would disappear. In some parts of Ireland, however, a cure could not be obtained so inexpensively. In her book, *Ancient Cures, Charms, and Usages of Ireland* (1890), Lady Jane Francisca Wilde, mother of Oscar Wilde, gives these directions for a sale of warts:—'Tie up some pebbles in a bag with a piece of silver money; whoever finds the bag and keeps the money, to him the warts will go, and leave you'.

Warts could be transferred to a variety of innocent animals, such as the

black slug in Oxfordshire and Buckinghamshire, or the toad in Lincolnshire and some states of the United States of America, or to plants. The ash tree, which is featured so prominently and so diversely in folk-lore, was connected with many of the superstitions concerning warts. In one of these the patient would address it thus:—

'Ashen tree, Ashen tree,
Pray buy these warts of me'.

He then took a pin, which he stuck first into the tree, then into the wart, and finally into the tree again, where it was left.

Another practice was to rub the wart with a bean shell, which was then secretly buried under an ash tree, to the accompaniment of the following charm:—

'As this bean shell wastes away
So my wart shall soon decay'.

In Cheshire, Sir James Frazer informs us in 'The Golden Bough', people rubbed their warts with a piece of bacon, which they then slipped under the cut bark of an ash tree. The warts would promptly vanish, to reappear as excrescences on the tree. One example may be cited of an inanimate object being victimized in this way: a piece of worsted was tied with as many knots as there were warts, and dropped down the lavatory. As the worsted decayed the warts were supposed to disappear.

An interesting letter from Tanganyika was recently published in *The Practitioner* (August 1950, p. 196). This contained a 'simple but effective remedy for warts: Rub the warts twice a day with the inside of the skin of the custard-apple. In a few days the warts will just drop off'. The following suggestion is also made: 'If warts are due to a virus infection it is possible that an extract from the custard-apple might be useful against virus diseases'.

A correspondent writes to me that as a boy of twelve years he was rather self-conscious as his hands were covered with warts. While on holiday in a village in Somerset, he consulted the local carrier and 'wart charmer', who asked him to count his warts carefully. Being told that there were twenty-four, he looked at him with his piercing blue eyes and assured him that these would disappear in four to six weeks. The boy, on leaving the house, found he had miscounted—there were twenty-five, not twenty-four warts. Six weeks later they had all vanished except one, which he has to this day.

REMEDIES HOLY AND UNHOLY

Remembering the warning in *Ecclesiastes* that there is no new thing under the sun, I spent a few instructive and amusing hours searching the literature for remedies holy and unholy, polite and unmentionable, with which the ingenious of old successfully exterminated disfiguring warts. Plant remedies are legion, with marked preference for those having a milky white sap. The more popular included juice of the dandelion, watercress, apple juice, Devil's milk (Yorkshire), the greater celandine—also called wartflower (Devon), wartwort (Gloucestershire and Wiltshire), or wartgrass (Cumberland, Yorkshire, East Anglia).

Professional wart charmers date back to at least classical antiquity. Sir Thomas Browne in his curious compilation 'Pseudodoxia Epidemica', remarks that old women were always famous for curing warts: 'they were so in Lucian's time'. In Cornwall the professional charmer would spit three times and breathe three times on the wart, muttering 'In the name of the Father, Son, and Holy Ghost, I bid thee begone'.

It is interesting to recall that Lord Bacon attributed the rapid decline of his warts to their having been rubbed with lard by the wife of the English Ambassador in Paris.

Among the quaint and queer substances recommended at divers times for local application may be mentioned liver and head of fish and scorpion, pig's and lizard's blood, human menstrual blood, fasting saliva, tobacco juice, dog's and dove's dung, and a piece of one's own skin.

The influence of the moon is seen in a number of popular remedies. In the 17th century Sir Kenelm Digby reported an 'infallible cure', which consisted of washing the hands by the moonbeams only in a well-polished silver basin in which there was not a single drop of water. An allied remedy was used in Cornwall, where these words had to be recited:—

'I wash my hands in this thy dish,
O man in the moon, do grant my wish,
And come and take away this'.

If a small piece of earth is taken from under the right foot, when the new moon is first sighted, made into a plaster, placed on the wart with a cloth cover and allowed to remain until the moon is out, the wart will be found to have disappeared (W. G. Black: 'Folk-Medicine', 1883). In Brittany, according to Frazer, the belief was prevalent that warts varied with the phases of the moon, growing as it waxed and vanishing as it waned.

Mark Twain's Tom Sawyer treated his warts at a ceremony which included the elegant recitation:—

'Spunk water, spunk water
Injun meal shorts
Spunk water, Spunk water
Swaller these warts'.

A religious flavour is found in the following examples. In Belgium the patient would visit a church to which he had never been before; he would dip his hands in holy water and dry them in the hooded clothes of an old woman. In Norfolk warty people would make the sign of the Cross on each wart with a pin or a pebble, which was then thrown away, and in Kent a victim would wet his forefinger with saliva and rub his warts three times in the direction of a passing funeral, saying: 'My wart goes with you'.

The successful employment of hypnotism in the removal of warts is mentioned in Ralph Slater's book 'Hypnotism and Self-Hypnosis' (1950), and the rôle of suggestion in treatment is discussed by H. Vollmer (*Psychosomatic Medicine*, 1946, **8**, 138).

CURRENT THERAPEUTICS

XXXVII.—LOCAL ANÆSTHETICS

By A. D. MACDONALD, M.D., M.Sc.
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It is nearly a century since Niemann (1860) isolated cocaine from the leaves of the South American plant, *Erythroxylum coca*. Its action in deadening sensation when applied to the tongue was soon appreciated, but the drug was first used in therapeutics in the treatment of the morphine habit—a treatment which merely added or substituted a second form of drug addiction. The anæsthetic use of cocaine in the eye by Koller (1884) was followed by infiltration and regional blocks, even including intrathecal use, for which the drug is quite unsuited (Corning, 1885).

COCAINE

Cocaine is still a 'first thought' when local anæsthetics are mentioned. When applied in low concentrations to nerve fibres and nerve endings it produces a sensory paralysis—first of pain, then of cold, warmth and touch, and lastly, of pressure, and a sensory paralysis as complete as can be obtained by nerve section, while in a mixed nerve, motor impulses can still pass. This order is believed to be related to the size of the nerve fibres concerned: the finer fibres are penetrated more easily and the drug is a local analgesic before it functions as an anæsthetic (Gasser and Erlanger, 1929). Its local action gains from its sympathomimetic effects. Cocaine potentiates the effects of the locally liberated adrenaline and hence acts as a vasoconstrictor. The dilatation of the pupil which follows its application to the conjunctival sac may be a disadvantage, in that intra-ocular tension may be raised. The mechanism of the anæsthetic action is still uncertain. We know that unlike the general anæsthetics which depress the permeability of the cell membrane, cocaine increases the ease with which water-soluble ions can pass into and out of the cell. It has been suggested that the local anæsthetic may affect the function of acetylcholine in impulse transmission, acting as an antimetabolite; but at present this is mere speculation.

Although cocaine is a potent local anæsthetic its value is limited by its local and systemic toxicity. Unnecessarily strong solutions produce neuritis and destruction of all exposed tissues, whilst the actions on the central nervous system and on the circulation have often led to misadventure. Even when small amounts have been used there is a possibility of idiosyncrasy leading to collapse and death, and when used repeatedly there is the risk of habit. A Committee of the American Medical Association recommended, accordingly, that cocaine should be administered only by the doctor and never to himself, that it should never be applied except to intact mucous membranes in doses which should not exceed 100 mg., and that special care

should be taken before applying cocaine to the urethra, because of the frequency of toxic sequelæ from such use (Mayer, 1924).

Besides the base and the hydrochloride, the B.P. 1948 provides a lamella, 1/50 gr. (1.3 mg.), and an oculentum (0.25 per cent.) for the eye; the lozenge, 1/20 gr. (3.2 mg.) cocaine, with krameria, 1 gr. (65 mg.), for the throat; and a suppository, $\frac{1}{4}$ gr. (16 mg.). The alkaloid may be incorporated in ointments for the relief of pruritus and other skin conditions, or in oily sprays (5 to 10 per cent.) for the throat. The hydrochloride, for which the *British Pharmacopœia* and the *British Pharmaceutical Codex* provide a recommended dose of $\frac{1}{8}$ to $\frac{1}{4}$ gr. (8 to 16 mg.), presumably to lessen morphine depression in the treatment of inoperable tumours, is used in 2 to 10 per cent. solutions for the eye, nose and throat. It is important to remember the dangers of the higher concentrations and to give the solution reasonable time to act. It is also important that the solutions should be freshly prepared and carefully sterilized, since the drug is readily broken down, losing its value but retaining its toxicity.

THE IDEAL

Since the limitations of cocaine became apparent, the search for the ideal local anæsthetic has proceeded almost continuously, and each year or two a new compound is added to the available list. It may well be that from the nature of the demands made, not one drug is required for all local anæsthetic uses, but an ideal for each. Before considering a drug to be in this class, however, the following properties would be expected:—

(1) Depression, rapid in onset and completely reversible in reasonable time, of sensory nerve fibres and endings by concentrations which do not injure surrounding tissues.

(2) Freedom from systemic toxic effects, at any rate when administered in the amounts required for anæsthetic purposes, i.e., a large margin between the toxic and the therapeutic doses. In the light of experience with cocaine, I would add freedom from idiosyncratic reactions.

(3) Water-solubility, stability in solution even when boiled for sterilization, and compatibility with adrenaline, since local anæsthetics are so often combined with this vasoconstrictor. The retention, however, in the *British Pharmacopœia* 1948 of the relatively insoluble benzocaine, butyl-aminobenzoate and orthocaine, presumably indicates that these are still in wide use.

SYNTHETIC LOCAL ANÆSTHETICS

Attempts to find the ideal have proceeded along various lines:—

(1) To find the active local anæsthetic part of the cocaine molecule in the hope that this nucleus would not carry the undesirable qualities of cocaine. Examples of such compounds are provided by tropacocaine, the eucaines, McElvain compounds, and perhaps Fourneau's amylocaine ('stovaine'). None of these, although pharmacologically interesting, has survived the sieve

of Pharmacopœial revision. Many would like to see cocaine similarly banished.

(2) Compounds derived from *para*-aminobenzoic acid. In addition to the sparingly soluble benzocaine, butyl-aminobenzoate ('butesin') and orthocaine, already referred to, which are used as powders or ointments to give sustained if limited action, three 'official' soluble compounds are provided in the hydrochlorides of procaine and amethocaine, and butacaine sulphate.

Procaine, also known as ethocaine and under numerous proprietary names—novocaine, neocaine, planocaine—is the diethylaminoethanol ester of *p*-aminobenzoic acid. Introduced by Einhorn in 1905, it is still the most widely used and one of the safest and most reliable of anæsthetics, except for mucous membranes, which the hydrochloride penetrates very poorly. Attempts to overcome this limitation have been made by preparing less readily ionized salts, such as borates (borocaine) and phosphates. These are unimpressive. Two official injections are provided, the stronger 2 per cent., the weaker 0.5 per cent. Both contain 0.002 per cent. adrenaline to limit spread and prolong the action. The drug is unstable in alkaline solutions, and solutions are best made up just before use. Operators handling procaine without gloves occasionally develop procaine-sensitivity dermatitis; but in the great majority procaine is singularly free from any irritant action and large amounts have been administered intravenously as a centrally acting analgesic.

Amethocaine (tetracaine, U.S.P.), *p*-butylaminobenzyl dimethylaminoethanol, is today perhaps still better known under proprietary names—pontocaine and decicaine. It is a much more powerful and more toxic anæsthetic, effective on infiltration in concentrations of 0.1 per cent. or less, and sufficiently effective yet non-irritant in higher concentration on mucous membranes to replace cocaine as a topical anæsthetic. An average dose for spinal anæsthesia would be about 20 mg. The action, as a rule, is twice or thrice as prolonged as that obtained with procaine.

Butacaine sulphate ('butyn') is slowly but freely soluble; an analogue of procaine, unsuitable for injection but effective for surface anæsthesia.

Cinchocaine ('nupercaine').—Of compounds not belonging to the cocaine or *p*-aminobenzoic acid groups, amylocaine ('stovaine'), although still used as a spinal anæsthetic, has been dropped from the *British Pharmacopœia*. Certain quinine and cinchoninic acid derivatives have long been used, and cinchocaine (Ciba's 'nupercaine', formerly 'percaine'—a dangerous original name because of its similarity to procaine—a very much less toxic drug) has been added to the *British Pharmacopœia*. No official monograph for an injection is provided, but cinchocaine is outstanding as regards potency and duration of action. Unfortunately it is also the most toxic of local anæsthetics, yet the ratio of toxic to therapeutic dose in this case is favourable, and it is much used for spinal and infiltration anæsthesia. Although a good surface

anæsthetic in the experimental animal, it is stated to be too irritant for use in the eye in man (Israels and Macdonald, 1931).

A recent introduction comes from Sweden under the name of 'xylocaine'. It has been given the 'approved name' of *lignocaine*. It is claimed to be quicker in action than procaine, but its duration of action is shorter and it is more toxic in both mice and rats. To this, and the many other local anæsthetics which although widely used have not been given the cachet of *British Pharmacopœia* recognition, space cannot be given in the present article—it would otherwise become a catalogue of drugs of varying history, convenience and value. The experienced surgeon is usually conservative in his choice of local anæsthetics; he knows what has stood up to the test of time and is little impressed by the manufacturer's latest blurb. During the war years, when service conditions emphasized the value and the dangers of this group, there was widespread feeling that cocaine and procaine, properly applied, were sufficient for all purposes. For more comprehensive reviews, see Hirshfelder and Bieter, 1932; and Keyser, 1950.

MEASURES FOR IMPROVING LOCAL ANÆSTHETICS

In the absence of an ideal local anæsthetic, attempts have been made along various lines to improve the action and safety of the drugs available.

Addition of adrenaline, to limit the spread, delay the absorption and reduce hæmorrhage. With many local anæsthetics, the action is surgically inadequate unless intensified and prolonged by the addition of adrenaline. Only small concentrations are required (0.002 per cent. or less for infiltration), and local damage may result from the use even of 0.005 per cent. Systemically also, adrenaline is potentially much more dangerous than most local anæsthetics, and might be fatal if given intravenously. It is probable that a good many calamities attributed to local anæsthetics are in truth due to adrenaline. It is not only in light $CHCl_3$ anæsthesia that intravenous adrenaline may induce fibrillation. On the other hand, adrenaline enormously reduces the toxic effects of local anæsthetics administered by infiltration, because of the slower absorption (Braun, 1903).

Mixtures of local anæsthetics have been used. There is no evidence of potentiation: the action of the mixture is the sum of the action of the components, and the use of such mixtures should probably be avoided.

Potassium salts.—These have some feeble local anæsthetic action in themselves, probably of no importance, but it has been recommended that anæsthetic solutions be made isotonic with 1 per cent. KCl instead of 0.9 per cent. NaCl.

Alkalinization of solution.—The anæsthetic bases penetrate more freely than the salts, so much so that it is claimed that in 0.5 per cent. $NaHCO_3$ solution the strength of cocaine for effective anæsthesia may be reduced by half. Some anæsthetics, such as cinchocaine, will not dissolve in alkaline

media, and others are rapidly reduced in action in such solutions, which should therefore be freshly prepared. The use of less highly ionized and buffered salts, such as borates and phosphates, depends upon similar principles. Reference has been made to the advantage of borocaines for mucous membranes.

Premedication.—It was established by Hofvendahl in 1921 that prior administration of hypnotics reduces the toxicity of local anæsthetics, and his observations have been extended by Tatum, Knoefel and their collaborators. The barbiturates seem especially to be suitable for this purpose, and considerably increase tolerance. Adequate premedication also reduces the psychical trauma of operation under local anæsthesia.

COMPARATIVE EFFICIENCY TESTS

Pharmacologists have exercised much ingenuity in evolving tests for the comparative efficiency of local anæsthetics. In the screening of new compounds, it is helpful to work out figures comparing the unknown with such established drugs as procaine and cocaine. The comparison may be made on capacity to produce block in the frog's or the rabbit's sciatic nerve, on the rabbit cornea, on intradermal wheals in guinea-pig, rabbit or man, and so forth. Before applying the figures for relative efficiency, they should be modified to take into account relative toxicity. This may be determined on subcutaneous, intramuscular or intravenous administration in mice and rats. The modifications provided by such measures as combination with adrenaline or premedication may be studied similarly. There is always a risk that when the tests are extended to man, drugs found satisfactory in the experimental animal may fail to live up to such reputation as they have earned in the laboratory (Eggleston and Hatcher, 1919; Macdonald and Israels, 1932).

Fate on absorption.—Absorption is usually slow. Large doses introduced suddenly into the circulation may paralyse the heart. If introduced more slowly, the main toxic effects fall on the respiratory centre, and artificial respiration is usually adequate for such depression. The short-acting local anæsthetics are rapidly broken down by esterases in the blood and liver, and disappear from the circulation in less than an hour. Cocaine persists in the tissues much longer, and is only slowly broken down. Cinchocaine is intermediate in its rate of clearance, at least in the cat. Liver damage is probably an important contraindication to the free administration of local anæsthetics.

CLINICAL USES

The clinical applications of local anæsthetics can be considered under three headings:—

Surface or 'topical' anæsthesia, for such mucous membranes as those of the eye, nose and throat. Cocaine (up to 10 per cent.) still leads in this field, but amethocaine (up to 2 per cent.) is being used more and more. For the oral

mucosa, Tainter and his colleagues (1937) recommended a 10 per cent. solution of benzocaine (in 70 per cent. alcohol), chlorbutanol, 'saligenin' or butacaine sulphate. For the urethra, 1 per cent. cocaine is used, provided no lesion is suspected. For unbroken skin, cinchocaine ointments are probably the nearest approach to a local anæsthetic.

Benzyl alcohol and 'saligenin' (*o*-hydroxybenzyl alcohol) have some limited use, e.g., in ointments for the relief of itch, and the former for mucous membranes. Solutions of thymol and ether in ethyl alcohol (Hartmann's solution) have also been used similarly, and for brief application to dental pulp.

Infiltration was popularized by Halsted (1885) and Schleich, and is often named after them. The official weak injection of procaine and adrenaline is used for extensive areas; the strong injection in the gums. The results are highly satisfactory, especially when freshly prepared buffered solutions are used. When a longer action is required, amethocaine (0.1 per cent.) may be substituted. Infiltration with solutions which contain no trace of adrenaline is rarely satisfactory. One interesting use of infiltration is in such conditions as fibrositis, when the pain is localized to precise points. Temporary local anæsthesia of such foci may rather surprisingly afford lasting relief, and a similar response may sometimes be obtained in such injuries as 'tennis elbow'. The mild injection of procaine is quite strong enough for such infiltration, which is usually followed by a course of massage and local applications of heat.

Regional or nerve block.—Here the nerve-trunks supplying the area are treated with the strong injection of procaine or an equivalent concentration of one of the other drugs. Accurate localization of the injection is necessary, otherwise anæsthesia may develop slowly or not at all. This, and such special cases of regional anæsthesia as spinal, where the drug acts on nerve roots within the theca, and paravertebral, trans-sacral, parasacral and presacral blocks, are problems for the surgeon or professional anæsthetist and hardly suitable for consideration here. There are several textbooks devoted to this practice. For an experimental account and references, see Hill and Macdonald, (1933, 1935), on spinal anæsthesia.

INTRAVENOUS PROCAINE

In the past ten years, procaine has been administered intravenously in man for a number of purposes: (1) as an analgesic in pruritus, the dressing of burns, and obstetrics; (2) quinidine-like (Dawes), to reduce cardiac irritability in arrhythmias, especially during operations on the heart, and to produce vasodilatation in vascular disease; and (3) in allergic states, including asthma, to act rather like the antihistamines. The action is not limited to procaine, but this has been preferred in man because of its ready destruction in the tissues and wide margin of safety. The drug is usually given in a 0.1 or 0.2 per cent. solution at a rate of about 15 mg./minute in a 70 kg. patient.

This should produce no feeling beyond a sense of warmth and relaxation. Higher rates of administration produce dizziness, drowsiness, and sometimes convulsions. The risk of untoward effects, as with local application, may be reduced by the administration of barbiturates. The analgesic action is claimed by Micks to be peripheral, since the concentration of drug found in inflamed or damaged tissues is substantially higher than in normal tissues, but Hewer and Keele have demonstrated that intravenous procaine will relieve pain in ischæmic muscle although none of the drug is reaching the muscle concerned, so much of the actions must be central (Robson and Keele, 1950). In view of the short duration of respiratory and other central depressions evoked by procaine in experimental animals, such clinical success is rather surprising unless the infusion be continuous. Since intravenous procaine may produce respiratory paralysis in doses which leave spinal reflexes relatively intact, apprehension must be felt about any suggestion of its use by this route as a general anæsthetic. A recent review of this field by Mushin and Rendell-Baker (1949) ends on a warning note: 'Vigilant supervision is necessary if overdose is to be avoided'.

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REVISION CORNER

THE SIGNIFICANCE OF TACHYCARDIA IN CHILDREN

THE term tachycardia means an abnormally rapid heart rate. This definition must have regard to the age of the patient, for the heart rate is not uniform throughout childhood. Normal heart rates at various ages are as follows:—

Age	Rate per Minute
Birth	120
6 to 12 months	115–105
2 to 6 years	105– 90
7 to 10 years	90– 80
11 to 14 years	80– 75

The sino-auricular node is the pacemaker of the heart but it is controlled by the varying degree of tone of the right vagus—parasympathetic—and in the newborn, vagus tone is minimal. It has been suggested that this in turn is due to the low arterial pressure in the newborn, and it is significant that as the blood pressure rises throughout childhood the cardiac rate falls.

ORIGIN OF TACHYCARDIA

Tachycardia is an accompanying feature of pyrexia; it is then an expression of increased metabolism. This article does not consider tachycardia of this nature, but deals with tachycardia occurring in the absence or virtual absence of pyrexia. Such tachycardia is almost invariably a sign of disease discovered on examination, and is not a symptom presented by the patient. It may be produced by a diminution in vagal tone, by increased sympathetic action, or by the advent of a new or ectopic pace-maker in the heart.

CARDITIS AND TACHYCARDIA

An impaired myocardium with its resultant diminished cardiac output and lowered blood pressure depresses vagal tone and produces a compensatory tachycardia. This may occur in the post-pyrexial period of a number of infections, e.g. diphtheria, influenza, and scarlet fever, but the most common cause in childhood is rheumatism.

Often the tachycardia is of insidious onset, and the child is brought to the practitioner because he is pale, more easily fatigued than formerly, is out of sorts generally, and is not eating well. It may be disclosed in the history that there have been headaches, perhaps pains in the limbs upon occasion—the so-called growing pains—or a susceptibility to throat infections. Epistaxis may have occurred more than once. Perhaps the practitioner has seen the child upon a previous occasion when there has been a complaint of abdominal pain which subsided following a period of rest in bed. He may then have considered a diagnosis of appendicitis, and indeed, such cases of rheumatism have been subjected to abdominal section. The physical examination will disclose not only the tachycardia, but also some

slight enlargement of the area of cardiac dullness; some indistinctness in the heart sounds, and perhaps the presence of a systolic murmur.

ANXIETY STATES AND TACHYCARDIA

The tachycardia of the bright, excitable, emotional child is of a different nature. Here the condition is functional and it is a question of overactivity of the sympathetic nervous system. Such children react violently to changes in their environment, even when these are of a temporary nature: for example, the absence, or anticipated absence, of a parent overnight: the anticipation of a journey, whether the journey be looked forward to with pleasure or fear.

A little boy lived in dread of being scalped when he learned he was to spend his summer holidays in Canada. Not only did he suffer from tachycardia, he could not sleep, he was irritable and restless; control over the urinary bladder became poor; his food was difficult to swallow, and he lost appetite. Yet he was active and betrayed no evidence of fatigue.

Such children do not readily disclose their fears; not even to their parents. This may be because they often realize the unjustifiable nature of their fears but feel they can do little about them. On this account it is essential that the practitioner should have the complete confidence of the child so that he may be able to go one better than the parent.

Unlike rheumatism, attacks of this nature tend to have a fairly sudden onset, are short lived though recurrent, and disappear with the passage of the anticipated event. Moreover, the tachycardia does not persist once the child has properly gone to sleep. Such children are often lacking in confidence, so that when another distasteful event appears to be imminent, the illness is repeated. Before making a diagnosis of functional tachycardia arising in an anxiety state it is essential to exclude the possibility of a hyperthyroid state on the one hand, and of paroxysmal tachycardia on the other.

HYPERTHYROIDISM AND TACHYCARDIA

Although uncommon in childhood, toxic goitre is by no means unknown in children, especially in girls and when over the age of ten years. The onset is usually gradual, and it has been observed to occur during convalescence from an acute illness, such as influenza or tonsillitis. Nervous manifestations are frequent early symptoms. There is excessive activity and excitability. There is tachycardia. The general behaviour may be suggestive of chorea, but the purposeful character of the activity is a distinguishing feature. A fine tremor is nearly always to be seen in the fingers of the extended hands. The warm moist skin is accompanied by flushing. The child is emotional and unstable.

In this early stage of hyperthyroidism, before exophthalmos and its accompanying eye signs have developed, there may be difficulty in differentiating a toxic goitre from a simple one, and a diagnosis of simple goitre in an excitable child may be entertained. In both conditions thyroid enlargement occurs early in the disease, and in both there is increased vascularity with its accompanying bruits and thrills. In these circumstances a count of the sleeping child's pulse is invaluable, for then the tachycardia of the excitable child will virtually disappear, whereas the tachycardia of hyperthyroidism will persist.

It should be remembered, too, that during adolescence, when the endocrine system is undergoing further development and readjustment, there may be some 'physiological' enlargement of the thyroid gland, and with it an accompanying tachycardia.

PAROXYSMAL TACHYCARDIA

Thus far, tachycardia has been considered mainly as an aid in diagnosis. In paroxysmal tachycardia the increased heart rate and its abrupt onset without apparent cause, in many cases, are the outstanding features of the condition. The attack appears to be started by some trigger mechanism, although this may be difficult to demonstrate. In some cases it may be of psychological origin: in others nausea and vomiting may be associated features. It may occur in the course of rheumatic heart disease or of hyperthyroidism.

It is not common in children, but it has occurred at all ages from the neonatal period onwards. The heart rate is regular and may be anything from 180 to 300 or more beats per minute. The beat is of ectopic origin, but may actually be a circus movement having a pathway through the sino-auricular or atrio-ventricular node. The duration of the attack varies, and if prolonged unduly, cardiac dilatation ensues and with it signs of congestive heart failure: dyspnœa, cyanosis, hepatic enlargement and œdema of the limbs. The speed with which cardiac failure develops will depend in large measure upon the state of cardiac efficiency before the onset of the attack.

This is a medical emergency, and although attacks usually cease spontaneously, and for as much reason as they began, every effort should be made to terminate the attack. In children, the application of a tight abdominal binder or flexing the trunk so that the head is between the knees, may terminate the attack. The application of cold water to the face or, in my experience, the drinking of cold water, may prove successful. The older child may be taught deep breathing with expiration against a closed glottis. The production of emesis, either by mechanical stimulation or by the administration of an emetic dose of ipecacuanha, may prove beneficial. The physician may endeavour to produce vagal stimulation by exerting strong pressure over the carotid sinus. Ocular pressure sometimes used in the adult is not likely to be tolerated by the child: it is painful.

When simple measures fail, and in any case if there are signs of the onset of congestive heart failure, the intravenous injection of acetyl-β-methyl-choline ('mecholyl') or carbaminoyl-choline ('doryl') may bring about a return to normal rhythm. These substances are nearly related to acetylcholine, which is the substance released at parasympathetic nerve ends when such nerves are stimulated. Acetylcholine itself is too easily broken down in the body to be of service. Other appropriate agents are quinidine, digitalis and quinine. Quinidine should be used with caution, for some children are intolerant of it.

MISCELLANEOUS

There remain to be mentioned some less common causes of tachycardia. Any mediastinal condition which gives rise to irritation of the vagus nerve will produce tachycardia. Enlargement of the mediastinal glands may cause it in childhood but other conditions, such as mediastinal fibrosis, intrathoracic neoplasm and aortic aneurysm, are rare. Anoxia, no matter what the origin, will also produce tachycardia; thus it is found in anæmic states and following hæmorrhage. Probably the rarest of all causes of tachycardia is thalamic tumour. The practitioner will also be mindful that certain medicines, not infrequently used in childhood, notably belladonna and thyroid gland extract, cause tachycardia.

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LINCTUSES

LINCTUSES are defined in the *British Pharmaceutical Codex* as 'viscous liquid preparations, usually containing sucrose and medicinal substances, which possess demulcent, expectorant or sedative properties. They are administered in doses of small volume and should be sipped and swallowed slowly without the addition of water'. The usual dose is 60 minims (3.5 ml.).

INDICATIONS FOR USE

The purpose for which a linctus is administered is to allay cough, and this is probably the most common symptom, apart from pain, from which relief is sought. The act of coughing must be regarded as a protective reflex intended to remove some source of irritation from the respiratory tract, but sometimes the respiratory mucosa is hypersensitive so that the cough reflex may be provoked by trivial stimuli. The reflex path consists of:—

(1) *Afferent fibres:* (i) Trigeminal nerve from the nose.
(ii) Glossopharyngeal nerve from the pharynx.
(iii) Vagus nerve: (a) from the larynx, lungs and external auditory meatus; (b) visceral and sensory fibres from the stomach and abdominal organs.

(2) *Reflex centre*, situated in the medulla close to the vomiting centre and sensory nucleus of the vagus. This may either be stimulated or depressed by drugs circulating in the blood.

(3) *Efferent fibres* to the muscles of respiration.

(4) *Higher centres*, which to some extent can inhibit the cough reflex but may also provoke coughing at will and influence its loudness and frequency.

The visceral sensory fibres of the vagus explain the causes of cough outside the respiratory tract, such as the 'stomach cough', and that which may be produced by wax in the external auditory meatus. In view of the fact that coughing is in most instances essentially a useful reflex, due consideration must be given to its cause and effect before attempting to subdue it entirely.

The purpose of the linctus is to suppress the troublesome, useless and unproductive cough, which may be painful or disturbing to the rest and sleep of the patient and, incidentally, to other members of a household or patients in a ward. It should, however, be remembered that equally effective for this purpose may be other preparations, such as inhalations, throat sprays, lozenges and pastilles, e.g.:—

Compound tincture of benzoin.
Compound lozenges of benzoin (B.P.C.)
Lozenges of liquorice (B.P.C.) 'The Brompton lozenge'.

Among the common indications for the use of a linctus are: coryza, pharyngitis and laryngitis; the early stages of bronchitis, influenza and pneumonia; dry pleurisy, pulmonary tuberculosis, and new growths of the lung.

LINCTUSES AVAILABLE

The index of Martindale's *Extra Pharmacopœia* lists twenty-six linctuses; in addition there are numerous proprietary preparations which come into this category, so that the prescriber has plenty of material with which to satisfy his personal choice. The B.P.C. includes eight, with three for infants; whilst the National Formulary (N.F.) reduces the number to three, and three for infants.

The following linctuses are in the B.P.C. (1949), but it should be noted that there are a number of changes in this group of preparations since the 1934 edition. The approximate amount of morphine, codeine or diamorphine, in each 60 minims, has been added after the dosage.

Name	Dose		Morphine, Codeine or Diamorphine per 60 minims (3.5 ml.)
	Minims	Millilitres	
Compound linctus of chloroform and morphine	30–60	1.8–3.5	1/20 grain (3.2 mg.)
Linctus of codeine, N.F.	30–60	1.8–3.5	1/8 grain (8 mg.)
Linctus of diamorphine	30–120	1.8–7.0	1/20 grain (3.2 mg.)
Linctus of diamorphine and hyoscyamus	30–120	1.8–7.0	1/20 grain (3.2 mg.)
Compound camphorated linctus of opium	30–60	1.8–3.5	1/150 grain (0.43 mg.)
Linctus of squill	30–60	1.8–3.5	
Opiate linctus of squill (Gee's linctus)	30–60	1.8–3.5	1/100 grain (0.65 mg.)
Simple linctus, N.F.	30–60	1.8–3.5	
Opiate linctus of squill for infants, N.F.	30–60	1.8–3.5	1/450 grain (0.14 mg.)
Simple linctus for infants, N.F.	30–60	1.8–3.5	
Compound linctus of tolu for infants, N.F.	30–60	1.8–3.5	

It will be observed that a number of these preparations, in addition to their demulcent properties, contain very small doses of drugs which depress the nervous mechanism of the cough reflex. It will also be noted that the linctuses containing diamorphine are no longer included in the National Formulary, an indication that their use is not generally considered desirable, since heroin, even in this dosage, can become a drug of addiction and should be employed with particular care, especially in cases with chronic cough, such as pulmonary tuberculosis. An equally powerful linctus is 'physeptone (brand) linctus' (B.W. & Co.), a D.D.A. preparation which contains 2 mg. of physeptone in each 60 minims (3.5 ml.).

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NOTES AND QUERIES

Alcohol and Infective Hepatitis

QUERY.—What evidence is there that alcohol is harmful to patients who have had infective hepatitis? If such evidence exists, for how long after an attack should they abstain?

REPLY.—There are numerous instances when men have gone on a drinking bout after recovery from infective hepatitis and have returned to hospital with a bad relapse. Hoagland and Shank (1946), working on sailors with jaundice, showed that hospitalization and restriction of activity appreciably shortened the period of convalescence, and that recrudescences commonly occurred after sick-leave. There is, however, no controlled experiment in which it was shown that men allowed to take alcohol were more prone to relapses and sequelæ than men who abstained. There is, nevertheless, suggestive evidence in favour of abstinence. Many people find their tolerance to alcohol reduced by an attack of infective hepatitis, and this happens in men in whom a hysterical perpetuation of the symptoms of the acute attack would not be expected. Biopsy has shown that the damage to the liver in infective hepatitis is much greater

than was formerly realized. Dible, McMichael and Sherlock (1943) found that 20 per cent. of cases showed histological damage of more than half the liver cells, and residual lesions were still present 21 to 51 days after the onset of the jaundice. It is usual to advise the patient to abstain from alcohol for six months after the onset of the jaundice.

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Aerophagy

QUERY.—In the article on flatulence and the use of carminatives (October 1949, p. 381), deglutition is referred to as a 'complicated neuromuscular feat . . . only mastered after considerable practice'.

(1) Can aerophagy (functional aerophagy and not a manifestation of organic disease) with gastric distension cause cardiovascular symptoms in an otherwise healthy individual?

(2) What measures can be taken to help patients suffering from 'functional' aerophagy to master the 'neuromuscular feat of deglutition? In other words how do we prevent air swallowing?

REPLY.—(1) There is no doubt that gastric distension—whether caused by food or by swallowed air is of no significance—can cause minor cardiovascular symptoms in otherwise healthy individuals. Palpitation is commonly complained of, and this may be connected with the presence of multiple extrasystoles. A certain amount of distress over the left lower chest and submammary region, which is wrongly attributed by them to the heart, is also experienced at times by these patients. Careful analysis of the pain, however, always reveals that no features of cardiac pain are present. I have occasionally encountered patients in whom attacks of paroxysmal tachycardia appear to have been precipitated by an excess of colonic gas.

(2) Patients with aerophagy are always quite unconscious of the fact that the air is being swallowed. A simple explanation to the patient is sufficient in some cases to relieve the symptom. The only other practical measure of any value is to render air swallowing impossible by getting the patient to place a solid object, e.g., a wine cork, between the teeth for half an hour after meals.

G. D. HADFIELD, M.D., F.R.C.P.

Word-Blindness

QUERY.—I have been told by experienced authorities that my son is 'word-blind'. He is eight, a fourth child, left-handed and intelligent. Please will you tell me about the ways to minimize this disability. Are there any probabilities about the sort of jobs he is likely to be suited for or to choose when he is old enough? I ask the latter question because it may influence the choice of school for him.

REPLY.—The first important point is to make sure that the difficulty in reading really is a specific aptitude defect, because the status of 'congenital word-blindness' as a clear-cut entity is at present under suspicion.

Children in whom difficulty in reading constitutes the major disability can often eventually be taught to read by a rather laborious and specialized type of training. If this is carried out with perseverance, in skilled hands, and so long as no other gross intellectual disorder exists, then an average level of educational attainment can be expected. The local educational authorities should be able to offer help as to the sources of this special training. Among the private schools which might cater for such a pupil are: Pierrepont House, Frensham, Surrey; Concord, Bexhill-on-Sea; St. Richards, Penmaenmawr; Salmon's Cross School, Reigate; and St. Mary's, Wrestwood, Bexhill-on-Sea. Should successful training be achieved, then most walks of life are open. If some disability still exists in the late teens, then vocational advice could be sought at that age from the Institute of Industrial Psychology (National), 40 Welbeck Street, London, W.1. Should, however, special education be impracticable, and the disability persist, then the choice is limited. Manual activities, farming, and artistic pursuits, seem the most promising. For an interesting autobiographical account of the handicaps of the word-blind sufferer, see *Brit. J. Ophthal.*, 1936, 20, 73. MACDONALD CRITCHLEY, M.D., F.R.C.P.

Effect of Barbiturates on the Respiratory and Cardiovascular Systems

QUERY.—The barbiturates apparently exert, on the one hand, a parasympathomimetic effect on the respiratory system (as evidenced by the increased irritability of the vagal, laryngeal and bronchial reflexes produced by thiopentone) whereas, on the other hand, they exert an antiparasympathomimetic effect on the cardiovascular system (as evidenced by the protection which they, e.g. thiopentone, afford against the vagal effects produced by cyclopropane). Can you explain the production of such opposite effects on two closely related parts of the autonomic (vagal parasympathetic) nervous system?

REPLY.—The effect of barbiturates on the

respiratory system and cardiovascular system varies with the particular animal to which they are administered, and also with the actual barbiturate used. The action of the barbiturates may be central or peripheral. The parasympathomimetic effect on the respiratory system is due to the central vagal stimulation (Burstein and Rovenstine, *J. Pharmacol.*, 1938, **63**, 42). Vagal depression, on the other hand, is due to the peripheral action of *certain* of the barbiturates, e.g. evipan sodium, pentobarbitone sodium, seconal sodium. But this vagal depression is not produced by the thiobarbiturates ('Pharmacologic Principles of Medical Practice', by Krantz and Carr). This is confirmed clinically, since cardiac arrhythmias and bradycardia due to cyclopropane cannot be prevented or arrested by the administration of thiopentone. For further information about the effect of the barbiturates on the autonomic nervous system, the reader is referred to 'Pharmacological Basis of Therapeutics', by Goodman and Gilman.

A. D. MARSTON, F.R.C.S., D.A., F.F.A., R.C.S.

Axillary Bromhidrosis

QUERY.—What is the simplest regime to cope adequately with the problem of under-arm perspiration and its odour?

REPLY.—This is a fairly common problem, but often, since proprietary preparations give relief, medical advice is not sought. Fœtid sweating, or bromhidrosis of the axillæ, is almost invariably associated with excessive sweating or hyperhidrosis. The fœtor may be due partly to saprophytic decomposition of the sweat, or partly to the secretion of the apocrine glands in this area. Although the endocrines seem to exercise predominant control over the apocrine glands, endocrine treatment is seldom successful in controlling any unpleasant odour due to apocrine secretions.

Hyperhidrosis is sometimes associated with indifferent general health, both physical and mental, and appropriate symptomatic treatment should be given. The control of bromhidrosis can often be achieved by local applications, but it may be necessary to try various preparations. Many such applications are liable to cause dermatitis, and the patient should be warned to discontinue their use if there is any soreness or irritation. These preparations should be applied after the axilla has been thoroughly washed with soap and hot water. The frequency of application needed varies from patient to patient, but about ten minutes three or four times a day is usually sufficient.

(1) 1-2 per cent. aqueous solution of sodium hexametaphosphate.
(2) 25 per cent. industrial spirit in lead lotion.
(3) 2 per cent aqueous solution of alum. If this is well tolerated, the strength can be increased up to 25 per cent.
(4) 1 :4000 aqueous permanganate solution.
(5) 1 per cent. solution of quinine in industrial spirit, or in eau de cologne.
(6) 1 per cent. formalin in equal parts of spirit and water. This is often very effective in controlling hyperhidrosis and bromhidrosis, but is particularly likely to cause dermatitis.

After the application of the appropriate lotion, a dusting powder, such as 3 per cent. salicylic acid in bismuth subgallate, should be applied. Rubber dress preservers should not be worn, since they are particularly likely to cause further excessive secretion and decomposition. When local applications fail, fractional dosage of X-ray may give relief, e.g., two applications of 200r at weekly intervals, followed by two similar applications after an interval of a month. If much larger dosage is given, there is a risk of causing radiodermatitis.

In rare instances when symptoms are dominating the patient's existence, it might be worth considering appropriate sympathectomy, but before suggesting this, a careful assessment would have to be made, especially of the patient's mental background.

H. J. WALLACE, M.D., M.R.C.P.

Persistent Migrainous Headache

QUERY.—A female patient of mine, aged fifty-two years, complains of headaches, migrainous in type and very severe, increasing in intensity and frequency. Investigations by a neurologist, a biochemist and a physician are all negative. The pain originates in the area of the second cervical vertebra, and radiates over one side of the head. It is controlled by 'femergin' injected at the beginning of the attack. No other form of medication has any effect. The injections are now required at least twice weekly. Can such frequency of these injections do any harm? Can any other form of treatment be suggested? Œstrogens, massage, manipulation, injections of novocaine, and ultra-short wave therapy, have all proved useless.

REPLY.—It is difficult to advise about this patient. The information given is not sufficient upon which to base a diagnosis. Migraine seems rather unlikely, and in the absence of physical signs the possibility of a functional disorder arises. It is assumed that there is no clinical or radiological abnormality of the cervical spine. The dose of 'femergin' is not mentioned, but it is generally considered wise not to repeat parenteral administration of ergotamine tartrate at smaller intervals than seven to ten days if prolonged use of the drug is contemplated. Perhaps a psychiatrist could help this patient.

DAVID KENDALL, D.M.

PRACTICAL NOTES

'Blackouts'

'"BLACKOUTS" are a common complaint in military neurological clinics, and need reasonable care in diagnosis, disposal and treatment', writes A. Barham Carter (*Journal of the Royal Army Medical Corps*, September 1950, **95**, 125), who records that in the Neurological Department of three military hospitals during the period April 1947 to April 1950, no less than 530 of the total of 1,344 out-patients seen complained of 'blackouts'. The diagnostic findings were as follows:—

Psychoneurotic attacks	240	(45.4 per cent.)
Syncopal attacks	120	(22.7 per cent.)
Epilepsy—major	90	
minor	8	(21.2 per cent.)
traumatic	5	
other types	10	
Migrainous attacks	26	(5 per cent.)
Aural vertigo	23	(4.3 per cent.)
Vasovagal syncope	6	(1 per cent.)
Hypoglycæmic attacks	2	(0.4 per cent.)

Of the 530 cases, 409 were National Service men, and 23 had rejoined after being invalided out of one of the Services previously. There were only 16 women in the series. Psychoneurotic attacks were the commonest cause of 'blackouts', which were variously described as: 'things go round', 'everything seems blurred', 'dizzy spells come on', 'I come over funny', and were brought on by excitement, worry, noise, and unpleasant environment. The author states: 'It was very difficult to distinguish this sort of reaction from malingering; even the most liberal judgment had to make this diagnosis in 2 cases'. The second type was the 'syncopal type', in which the patient sank to the ground but was able to save himself injury; unconsciousness was rarely complete. The third form was the 'hysterical convulsion', with sudden onset, always in the presence of company. The fourth type was the 'post-concussional syndrome', with a history of previous head injury. The milder cases respond to reassurance and explanation of their illness in relation to their environment. They are returned to full duty. The hysterical convulsion group should be referred for psychiatric opinion. The post-concussional patients require head exercises immediately on regaining consciousness, and explanation that keeping their head still and developing 'head consciousness' are the cause of their complaint. Syncopal attacks, or fainting, can often be prevented by bending the head down; these men are returned for full duties, but if a driver, relief from this duty is advised. Ephedrine, ½ grain (32 mg.), is worth trying, or simple smelling salts, coupled with reassuring the patient that his brain is normal. (This applies when physical examination and X-ray of chest and urine testing are negative.) Patients with vasovagal syncope and hypoglycæmic attacks usually require invaliding from the Service, as also cases of major and minor epilepsy. Cases of traumatic epilepsy and other types may sometimes be retained in a lower medical category, particularly those who have sustained penetrating brain lesions and have made a good recovery. Some cases of one attack of *grand mal* (diagnosed 'convulsion N.Y.D.') or perhaps two attacks with a year's clear interval between, should be placed in category P6 or P7, i.e., not to drive and not to handle lethal weapons. Mild cases of migraine respond to codeine, fresh air and exercise; moderate cases should be recommended for categories P5 or P6, as tropical climates may make them severe; severe cases may need invaliding from the Service. The mild forms of labyrinthine vertigo respond to phenobarbitone or small doses (1/200 grain—0.32 mg.) t.d.s. of hyoscine hydrobromide, and advice to avoid sudden change of position; moderate cases need downgrading to P5, 6 or 7; it is stated that 'only very few were invalided out'.

Irradiated Para-Aminobenzoic Acid in Rheumatic Conditions

USING solutions of the sodium salt of *para*-aminobenzoic acid (PABA) which had been exposed to ultra-violet irradiation, A. El-Mofty and M. Bassiouny (*Journal of the Royal Egyptian Medical Association*, 1950, **33**, 617) have treated a series of patients with different rheumatic conditions, a smaller series treated with non-irradiated sodium salt of PABA being used as controls. Ten cases of rheumatic fever received the irradiated preparation in dosage of 1 to 3 g. daily: in seven cases fever subsided within one to seven days and pulse rate gradually declined, as also the sedimentation rate; the joint pains disappeared with improvement in pulse and temperature. In three cases the fever and joint pains subsided but tachycardia persisted: in one case there was a favourable response and the pulse rate declined from 100-110 to 80 in one week; in the other two cases no appreciable effect on the pulse rate was noted. Eight cases of fibromyositis were treated: six responded favourably in about one week. Three cases of rheumatoid arthritis all responded favourably as regards the pain, as also did four cases of periarticular fibrositis associated with osteoarthritis of the knees; movement in these latter cases also became easier. In the control series receiving non-irradiated PABA (3 rheumatic fever, 2 rheumatoid arthritis, 2 fibromyositis)

no definite improvement was noted with dosage double the amount of the irradiated form. In conclusion it is stated: 'From this preliminary report, one can certainly conclude that after irradiation PABA has gained definite potentialities towards the above-stated rheumatic conditions'. Further work is to be carried out.

Chloramphenicol in Hæmophilus Influenzæ Meningitis

FIFTEEN consecutive cases of *H. influenzæ* type B meningitis in children of ages ranging from six weeks to nine years have been treated with chloramphenicol, and the results of the treatment are recorded by G. W. Prather and Margaret H. D. Smith (*Journal of the American Medical Association*, August 19, 1950, **143**, 1405). *H. Influenzæ* was identified by direct smear and Neufeld's reaction in all cases, and in twelve was later confirmed by culture. Eight of the patients had received sulphonamides or antibiotics before admission to hospital. Chloramphenicol was given in initial dosage of from 42 to 111 mg. per kg. body weight, followed by 250 mg. eight-hourly regardless of body weight. The drug was given orally in all but one case, in which rectal administration was necessary. Duration of treatment varied from five to fourteen days. The first four patients admitted received in addition to the chloramphenicol a type-specific antibody: rabbit antibody nitrogen, 175 mg., 100 mg.; the last two cases 150 mg. each. This was given as the efficacy of chloramphenicol in *H. influenzæ* meningitis was unknown at the beginning of the series. All 15 patients recovered, although persistent vomiting, bulging fontanelle and convulsions occurred in three cases during convalescence. In another case fever, dyspnœa and anorexia persisted and the child developed pneumonia; treatment with sulphadiazine, penicillin, streptomycin and anti-influenzæ type B rabbit antibody was given. Another child had persistent fever, and two children transient arm and leg muscle weakness. All recovered eventually. It is stated in conclusion that in each case the spinal fluid was sterile on second lumbar puncture, and no toxic effects attributable to the drug were noted. A dosage scheme of 50 to 100 mg. per kg. body weight by mouth or stomach tube on admission, followed by 250 mg. eight-hourly for five or more days, regardless of weight, is suggested.

Chiggers and Jiggers

THE chigger or jigger (sand-flea—*Tunga* or *Dermatophilus penetrans*) is a common pest in tropical areas, parts of America, the West Indies, West and East Africa, and recently India. The flea (fig. 1), which lives in dry sandy soil, attacks and lives on all warm-blooded animals, including man. The female when

FIG. 1.

FIG. 2.

pregnant burrows under the skin of its host leaving only the rear segments visible. As ovulation proceeds the abdomen swells and the insect becomes round like a pea (fig. 2) and produces a nodule in the victim's skin, around which a blister develops. When the eggs are expelled the jigger shrivels up, is sloughed off, and leaves a small ulcer, which if not treated may lead to secondary infection. The unusual occurrence of a case in this country is described by H. P. Ford (*The Chiropodist*, November 1950, **5**, 315). The patient, a male, had been to East Africa on a business trip, returned by air, and some three days later developed severe pain in the fourth toe of the right foot. On examination there was a large blister under the nail with a small black speck in the centre (the rear segments of the jigger). Treatment consists in removing the jigger intact by cutting round the edge of the blister and lifting off the top to which the insect should be attached. The ulcer is then cleansed with a weak solution of dettol, and an antiseptic dressing (1:1000 acriflavine) is applied. If a portion of the insect should be left it should be touched with a drop of pure phenol to minimize the likelihood of secondary infection.

Pneumothorax and Interstitial Emphysema in Asthma

'PNEUMOTHORAX in asthmatics may be commoner than generally recognized; a sudden critical increase in dyspnœa, and cyanosis, or pain confined to one side of the chest should direct inquiry in this direction', write H. S. Mitchell and H. L. Bacal (*Canadian Medical Association Journal*, November 1950, **63**, 467), who record three cases, two of which proved fatal. In one case, a child of three years, there was no pneumothorax, but death resulted from interstitial emphysema. In the second fatal case there was a left-sided pneumothorax, which disappeared spontaneously, but was followed by subcutaneous emphysema, from which the patient, a woman of thirty-eight, died. In the third case, a man of twenty-nine, there was pneumothorax which responded to treatment;

generalized interstitial emphysema did not develop in this case. The signs of the occurrence of a pneumothorax are: sudden increase in dyspnœa; pain in one side of the thorax; change in the character of the cough; cyanosis; and collapse. Mediastinal emphysema is evidenced by crunching or creaking in the chest, signs of circulatory embarrassment, and the characteristic physical signs of the condition. As a rule the prognosis in interstitial emphysema and pneumothorax is good; but in asthmatics it is less favourable. Treatment consists in rest and no mechanical interference with the pneumothorax; but when increasingly deep cyanosis and collapse are present, reduction of the pneumothorax tension is indicated. Aspiration of air from the mediastinum, and removal of bronchiolar plugging by mucus provide measures of relief, and when pneumothorax is recurrent, obliteration of the pleural space by simple technique is indicated. 'Hydration, iodides, relief of bronchiolar spasm, and especially prompt bronchoscopic aspiration, are probably of as great importance as control of pressure effects of interstitial emphysema or pneumothorax'.

Trasentin in Gynæcology

A PRELIMINARY report by D. B. Gershenfeld *et al.* (*American Journal of Obstetrics and Gynecology*, September 1950, **60**, 658) suggests that 'trasentin' is of value in the treatment of dysmenorrhœa and of spasm of the Fallopian tubes, and for aiding cervical dilatation in the first stage of labour. Trasentin, which is the trade name for the hydrochloride of diphenylacetyldiethylaminoethanol, acts by relaxing smooth muscle spasm both directly and by depressing parasympathetic action. In 5 patients undergoing Fallopian tube insufflation it was given in doses of 100 mg. intramuscularly, thirty to sixty minutes before insufflation. All five had had previous insufflation without successful passage of gas through the tubes. Following trasentin, insufflation was successful in four cases; in the fifth, organic tubal occlusion was later demonstrated. To 25 cases of dysmenorrhœa it was given either intramuscularly in doses of 100 mg., or orally in doses of 150 mg., to a daily total dose of 600 mg. Complete relief was usually obtained, but this was more likely to occur with intramuscular administration than when given orally, and if the drug was given before the peak of the pain was reached. For dilatation of the cervix in the first stage of labour, trasentin was given intramuscularly in doses of 100 mg. in patients 'whose progress in cervical dilatation had become static for two to six hours'. In most of the cases 'a very dramatic improvement in cervical dilatation' occurred within thirty to sixty minutes. No side-effects were observed in any of the patients treated with trasentin.

The Cast Syndrome

THE 'cast syndrome' consists of persistent vomiting and dilatation of the stomach in a patient to whom a body cast has been fitted. In describing one case, a girl aged eighteen years, which proved fatal, M. H. Dorph (*New England Journal of Medicine*, September 21, 1950, **243**, 440) states that apparently only four other cases have been recorded, three of which proved fatal. In his case, necropsy revealed dilatation of the stomach and of the duodenum up to the ligament of Treitz, where there was an abrupt reduction in the diameter of the intestine. No evidence could be found of an organic obstructive lesion. The conclusion drawn from this case, and the others recorded, is that 'the greatest care must be exercised in the treatment of patients in body casts who present the symptoms of persistent vomiting and gastric dilatation. This precaution consists of immediate gastric intubation, removal of the entire cast, if necessary, and strict regulation of body fluids as indicated from laboratory and clinical findings'.

Podophyllin for Senile Keratoses

THE use of podophyllin for the treatment of senile keratoses is recommended by A. Fletcher Hall (*Archives of Dermatology and Syphilology*, September 1950, **62**, 362). Light curettage of the surface of the keratosis is first carried out, without anæsthetic. If much bleeding results, this is controlled by pressure with a gauze square. The podophyllin solution (25 per cent. podophyllin and 20 per cent. salicylic acid in equal parts of acetone and 95 per cent. alcohol) is pressed on by means of a saturated cotton-tipped applicator for 15 to 30 seconds. This produces a certain amount of stinging. The treated lesion is allowed to dry. Should bleeding occur, further pressure is applied and the lesion is retouched with the solution. The patient is instructed not to wash over the treated area for twelve hours, and is warned that it will remain red and tender for about a week. He is seen again in a fortnight, when any remaining crusts are peeled off. In the case of keratoses near the canthi of the eyes, intense conjunctivitis and keratitis may occur even in cases in which the utmost care has been exercised to prevent any of the solution getting into the eye. Keratoses of the hands and fingers do not respond well to this treatment unless they are 'unusually superficial'. 'In view of the fact that others have found this method adequate in the treatment of skin cancer, it is felt that it may be considered safe in the treatment of precancerous lesions'.

REVIEWS OF BOOKS

Rest and Pain. By JOHN HILTON, F.R.C.S., F.R.S. Edited by E. W. WALLIS, M.D., B.Sc., and ELLIOT E. PHILIPP, M.B., M.R.C.O.G. London: G. Bell & Sons, Ltd. 1950. Pp. xxxiv and 503. Figures 105 and 2 plates. Price 25*s.*

HILTON'S 'Rest and Pain' is one of those books which every doctor has heard of, but few have read. The publication of this book (technically the sixth edition) should go far towards rectifying this regrettable state of affairs. In preparing this edition the original text has been retained, but at the end of each chapter the editors have added notes summarizing current views on the matter discussed by Hilton. This is an excellent innovation as it does not interfere with the characteristically clear manner in which Hilton presented the subject, but yet allows the reader to appreciate those points in which Hilton's views have been modified by subsequent investigations. The value of this book has also been greatly enhanced by the inclusion of an admirable biography of Hilton by Mr. Hedley Atkins. The editors are to be congratulated on the skill with which they have carried out their task of re-introducing this major surgical classic to the profession. It is now up to the medical teachers of the country to ensure that no student shall pass through their hands without having studied it.

Pain and Its Problems. Edited by Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S., and WILLIAM A. R. THOMSON, M.D. London: '*The Practitioner* Handbooks'; Eyre and Spottiswoode (Publishers) Ltd., 1950. Pp. 194. Price 12*s.* 6*d.*

IF modern custom dictates an attitude towards reviewing a book it is one of being coldly objective. As a clinician I find it difficult to avoid a little enthusiasm about this latest addition to *The Practitioner* Handbooks.

Lord Moran reminds us that pain is a common symptom. He might have said with truth that pain is by far the most common of all symptoms. It therefore follows that without a careful study of pain, in its anatomical, physiological and psychological relations, the physician cannot hope, in the majority of cases presented to him, to solve the problem of diagnosis, which is the be-all and end-all of clinical medicine. On the other hand, if he listens patiently to the patient's story—a *sin qua non* in the investigation—and relates this to a knowledge of nerve paths and centres, and experience, he can frequently get very near to a correct answer of the question at issue.

Teachers of medicine are often asked to suggest to their students a list of textbooks which it is advisable for them to read. I was myself accustomed to head the list with Jevons' 'Primer of Logic'; I forget what book I put next, but I am sure that if the present work on Pain had been available at the time I should have given it high priority on the list. The Editor has chosen his team, not only with care to cover the field adequately, but with intimate knowledge of their individual claims to present the particular aspect of the subject allotted to them. It would be invidious to single out any one contribution when all are so good. Nor have I much to say by way of criticism. The chapter on 'Pain in (*sic*!) the Gastro-Intestinal Tract' is perhaps a little summary in its content, bearing in mind how largely it bulks in actual practice and its importance in relation to ground that is so often common as between physician and surgeon. But in view of the great value of the book, both to the student and to the practitioner, I feel apologetic in mentioning even this, to me, slight defect.

HORDER

Textbook of Physiology and Biochemistry. By GEORGE H. BELL, M.D., B.Sc., F.R.F.P.S.G., F.R.S.E., J. NORMAN DAVIDSON, M.D., D.Sc., F.R.F.P.S.G., F.R.I.C., F.R.S.E., and HAROLD SCARBOROUGH, M.B., PH.D., F.R.C.P.ED. Edinburgh: E. & S. Livingstone Ltd., 1950. Pp. x and 918. Figures 55. Price 45*s.*

PHYSIOLOGY and biochemistry have become so vast that it is doubtful if they can be adequately dealt with in a single textbook. On the other hand, the medical student today has too little time for reflection; he welcomes a factual exposition. This is a pity, and the situation is not without danger. Progress comes from the inquiring mind, and the appropriate stimulus is the experimental approach. Yet if one were to marshall and attempt to evaluate all the evidence upon which the body of physiological and biochemical knowledge is founded, a volume of some 900 pages would be but a beginning. Nevertheless, the authors are to be congratulated on completing a task which few of their colleagues would have been willing to undertake. At times the book is didactic; some may feel that portions of the subject are less fully dealt with than they might have hoped. It has, however, the great advantages of unity of outlook. An outstanding feature is the wealth of carefully chosen, well-reproduced illustrations, which is unique. In a disarming preface the authors claim that the book is intended as

an introduction. It is indeed a full one and should serve well the needs of medical and dental students.

Textbook of Venereal Diseases. By R. R. Willcox, M.B., B.S., London: William Heinemann (Medical Books) Ltd., 1950. Pp. 439. Figures 154 and 7 colour plates. Price 32*s.* 6*d.*

As the preface states, this textbook differs from all others . . . 'in its wide global outlook. It is not confined to those conditions familiar to temperate climates, but includes in its pages all the tropical and subtropical venereal infections which are generally ignored in conventional works'. This outlook undoubtedly results from the exceptionally wide experience of Dr. Willcox as a Command Specialist in Venereal Diseases in West Africa, and from his post-war surveys in Southern Rhodesia, the Middle East, and Pakistan. Dr. Willcox has admirably carried out the task he has set himself: the book is well planned with adequate clinical descriptions of the venereal diseases, the spirochætoses of the tropics or subtropics resembling syphilis, and the many other genito-urinary conditions commonly referred to venereal diseases clinics. The advice as to their treatment is equally sound. This book can be thoroughly recommended and should have a deserved success among venereologists, not only in this country, but equally abroad.

Recent Advances in Physical Medicine. Edited by Francis Bach, D.M., D Phys. Med. London: J. & A. Churchill Ltd., 1950. Pp. xv and 490. Figures 93. Price 27*s.* 6*d.*

The functions of the physical medicine department of a general hospital are, according to one of the contributors to this symposium: first, *physiotherapy;* secondly, the preventive *physical training* of children and adolescents (as another contributor points out, a fortunate twist of the word 'physical'); and thirdly, *rehabilitation* of the man or woman likely to become permanently disabled. Recent advances in this somewhat untidy subject are not easily assembled in the form of a readable book. Dr. Bach has made his task more difficult by asking as many as 38 authors to write it, and by not restricting them to recent advances, with no more than a brief historical account of the base from which advance has been made. The student of physical medicine, for whom the book is intended, will, however, find much useful information in it. Especially worthy of notice are chapters on electro-magnetic waves, on electro-diagnosis, and on the organization of a physical medicine department. Rehabilitation is itself a recent advance, and a recent addition to the function of physical medicine. The section devoted to it will be found well worth reading.

Significance of the Body Fluids in Clinical Medicine. By L. H. Newburgh, M.D., and Alexander Leaf, M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1950. Pp. vii and 76. Figures 16. Price 15*s.*

This book in the American Lecture Series is a concise and lucid account of the part played by the body fluids in clinical medicine. The authors assume, perhaps wisely, an ignorance of functional vocabulary, and in the opening chapter explain clearly the activities of electrolytes as regards both their equivalence and valency. The phenomenon of osmotic pressure is also explained by diagrammatic illustration. The work is divided into two main headings, namely, Physiology and Clinical Significance. In the former, after the discussion of functional units, the composition of body fluids, both intra- and extra-cellular, the adjustment of pH and respiratory regulation are reviewed. In the latter part, abnormalities of pattern, again extra- and intra-cellular, are discussed, and the whole rounded off with the consideration of water balance, œdema and dehydration, with detailed consideration of œdema in nephritis. This book is of considerable value to both students and practitioners.

Toxæmias of Pregnancy: Human and Veterinary. (A Ciba Foundation Symposium.) Edited by John Hammond, D.Sc., F.R.S., F. J. Browne, M.D., D.Sc., F.R.C.S., F.R.C.O.G., and G. E. W. Wolstenholme, O.B.E., M.B. London: J. & A. Churchill Ltd., 1950. Pp. xii and 280. Figures 93. Price 21*s.*

This little book is a matter for congratulations: to the Ciba Foundation for the inception and carrying out of the original idea of gathering together from the quarters of the world a group of distinguished and active workers in a given field to discuss the many facets of a difficult problem; to the contributors who brought the fruits of their research and experience and made valuable and concise communications; to the publishers for making these available to all interested or working in this field. This book should be read by all obstetricians or those interested in the toxæmias of pregnancy. It would be invidious to single out any special contributions for mention as all bear the mark of authority and distinction, although the physio-

logical and pathological sections are most welcome. It would have been useful if more of the discussion had been available, and the summaries seem rather short. This is the first such symposium. We look forward to others.

Introduction to Motherhood. By GRANTLY DICK READ, M.D. London: William Heinemann (Medical Books) Ltd., 1950. Pp. xii and 92. Figures 21. Price 6*s*.

THIS is a simple, practical book for intending mothers. In addition to the author's now widely known views on natural childbirth, there are chapters on simple anatomy, on the physiology of conception and pregnancy, on different aspects of antenatal care and exercises, breast feeding, and the care of the baby. There is much useful, sensible advice set out in these pages which is none the less valuable for the rather heavy emphasis on the emotional aspects of motherhood. Dr. Dick Read's enthusiasm has inspired countless mothers from all parts of the world, and the complete satisfaction so many have known when following his methods calls for the attention his books deserve.

Lehrbuch der Chirurgie. Volume 2. EDITED BY A. BRUNNER, C. HENSCHEN, H. HEUSSER, A. JENTZAR, O. SCHÜRCH and J. VEYRASSAT. Basle: Benno Schwabe and Co., 1950. Pp. xx and 2037. Figures 448. Price Sw. frs. 76.

THIS is not a book to criticize but to admire, for the print is good and clear, the illustrations are numerous and apt, and the subject matter and teaching are well abreast with current views. This volume deals with the surgery of the face and neck, the thorax, breast, intestinal tract, the liver, spleen, and pancreas, the genito-urinary organs, the spinal column, the extremities (including fractures), and the autonomic nervous system. Although many names are mentioned no references are inserted and in some cases names are not spelt correctly, e.g. Keyens for Keynes. The section on the breast is rather short and cancer of that organ is disposed of in 12 pages, whilst hæmorrhagic and acute pancreatitis occupy almost as large a space (10 pages). The latter article is, however, an excellent contribution. This textbook can be recommended to all who wish to keep by them a well produced book giving a good and clear account of present surgical knowledge.

NEW EDITIONS

MUCH new material has been added to *The Pathology of Internal Diseases*, by William Boyd, M.D., F.R.C.P., F.R.C.S., in its fifth edition (Henry Kimpton, 77*s*.): there is an entirely new chapter devoted to diseases of the bones and joints, and the numerous subjects covered in new sections include cortisone (compound E) in arthritis, congenital hæmolytic disease, the anæmias of infection and those due to folic acid deficiency, choline deficiency hypertension, Lœffler's pneumonia, pulmonary moniliasis, anthraco-silicosis, beryllium and bauxite pneumonitis. Space is too limited to enumerate all the new material; in addition much rewriting has been undertaken, for example, in the sections on congenital abnormalities of the heart, and poliomyelitis. The new edition is well and generously illustrated, containing, in all, 391 figures and 11 coloured plates.

A Handbook on Diseases of Children, by Bruce Williamson, M.D., F.R.C.P., in its sixth edition (E. & S. Livingstone Ltd., 17*s*. 6*d*.) has been revised and brought up to date. A number of advances in pædiatrics have been made and become established since the appearance of the fifth edition in 1947: the use of streptomycin in tuberculosis and tuberculous meningitis, and the institution of B.C.G. vaccination—this chapter on tuberculosis is well conceived; Brock's operation for relief of the stenosed pulmonary valve in the treatment of 'blue babies'; the use of penicillin in ophthalmia neonatorum. These are but a few of the new items which have been added to the new edition of this useful handbook of children's diseases.

Common Skin Diseases, by A. C. Roxburgh, M.D., F.R.C.P., in its ninth edition (H. K. Lewis & Co., Ltd., 25*s*.) contains sections dealing with BAL, the antihistamine drugs, the use of streptomycin in conjunction with calciferol in lupus vulgaris, penicillin and mepacrine dermatites, vitiligo, lichen sclerosus vel atrophicus, and Senear-Usher pemphigus. There is a valuable section on ointment bases. The new edition is beautifully illustrated, and contains many useful formulæ.

Practical Neurological Diagnosis, by R. Glen Spurling, M.D., in its fourth edition (Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 37*s*. 6*d*.) has been submitted to general revision and some rewriting. A new section on the hypothalamus has been added, and also a useful glossary of terms commonly used in clinical neurology. The new edition is well illustrated, and particularly in the chapter on roentgenologic diagnosis, which contains a number of good reproductions of skiagrams.

The contents of the February issue, which will contain a symposium on 'Midwifery in General Practice', will be found on page lxviii at the end of the advertisement section.

Notes and Preparations, see page 101
Fifty Years Ago, see page 105.

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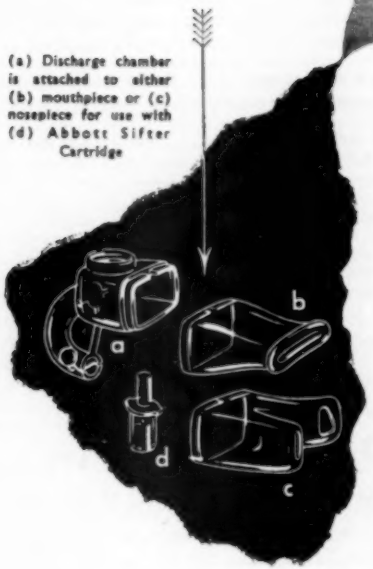

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* The Inhalation of Penicillin Dust, *J. Amer. Med. Assn.* 138 : 344, October 2, 1948.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

ABBOCILLIN R/R (rapid/repository penicillin aqueous) consists of the crystalline procaine salt of penicillin G and buffered crystalline penicillin G potassium, combined with approximately 0.5 per cent. sodium carboxymethyl-cellulose and 0.1 per cent. sorethitan monooleate as suspending and dispersing agents in the final solution. After addition of the amount of water for injection or sterile isotonic sodium chloride solution specified on the label, the resulting suspension contains 400,000 units of penicillin in each ml. The use of Abbocillin R/R Penicillin Aqueous is indicated in cases in which repository penicillin is effective, and particularly in those in which frequent repeated injections are inadvisable or impossible. Issued in 1-dose vials (penicillin G procaine 300 000 units, and penicillin G potassium 100,000 units) and 5-dose vials (penicillin G procaine 1,500,000 units, and penicillin G potassium 500,000 units). (Abbott Laboratories Ltd., Wadsworth Road, Perivale, Greenford, Middlesex.)

ALUPHOS is a pleasantly flavoured preparation containing 7½ per cent. w/w of aluminium phosphate prepared for use in the treatment of peptic ulcer. The advantages claimed for this preparation are: it is non-constipating; it neutralizes excess acid but does not inhibit peptic acitivity; the phosphate ion is said to have an almost specific action on flatulence; it does not interfere with the absorption of phosphate or vitamins from the gut. Aluphos is issued in bottles of 6 and 80 fluid ounces. (Benger Laboratories Ltd., Holmes Chapel, Cheshire.)

DESOXYNE (*d*-desoxyephedrine hydrochloride—'methamphetamine hydrochloride Abbott') has been prepared for oral administration in the treatment of narcolepsy, mild depression, as a temporary mental stimulant, and as an adjunct to the treatment of obesity. It should not be administered to patients of advanced age, or to those with insomnia, cardiovascular or thyroid disturbance, or of a neurotic or hyperexcitable nature. Desoxyne is issued in bottles of 25 and 100 tablets of 2.5 mg. (Abbott Laboratories Ltd., Wadsworth Road, Perivale, Middlesex.)

DIN-DIN LIVER PURÉE FOR BABIES contains protein 13 per cent., fat 3.2 per cent., and carbohydrate 3.7 per cent. It is composed of the fresh livers of healthy pigs, 'passed for human consumption by Government Veterinary Inspectors, heat processed, and made assimilable for an infant's digestion'. 'Din-Din Liver Purée' can be introduced in baby's diet at the age of five to six months when the beginning of a mixed diet is indicated, or earlier, reinforced with calcium, for allergic infants when milk is excluded from the diet. Issued in hermetically sealed glass jars of 3 ounces. (Antigen Ltd., Roscrea, Ireland: Distributors: Din-Din Ltd., 5 Rampayne Street, London, S.W.1.)

GANTRISIN (3,4-dimethyl-5-(p.aminobenzenesulphonamido)-isoxazole, or 3,4-dimethyl-5-sulphanilomido-isoxazole, or NU-445) is a readily soluble sulphonamide which is effective against gram-negative and gram-positive organisms. It is stated to be of low toxicity and to produce relatively few side-reactions. Its use is indicated in the treatment of urinary infections due to *B. coli*, *B. proteus* and *B. pyocyaneus*, and in systemic infections due to streptococci, staphylococci, pneumococci, gonococci and *B. coli*. 'Gantrisin' is available in tablets of 0.5 g., in packings of 20 and 100. (Roche Products Ltd., Welwyn Garden City, Herts.)

IRGAPYRIN is a combination of butazolidine sodium salt (3:5 dioxo-1:2 diphenyl-4-*n* butylpyrazolidine) with amidopyrine, and is available as a solution containing 15 per cent. of each compound and having a pH of 8.2. It is stated to possess 'marked anti-inflammatory, analgesic and antipyretic properties', and has been used with success in the treatment of rheumatism and in inflammatory conditions of the eye. Irgapyrin is administered intramuscularly and is issued in ampoules, each containing amidomyrine B.P. 12½ grains and butazolidine 12½ grains in 5 ml. sterile solution, in boxes of 5 and 50. (Pharmaceutical Laboratories Geigy Ltd., National Buildings, Parsonage, Manchester 3.)

MYLIPEN is a ready prepared aqueous suspension of procaine penicillin, containing in each ml. 300,000 units of procaine penicillin, with 2 per cent. dispersing agents and 0.025 per cent. cetrimide, a bacteriostatic and wetting agent. With this preparation the inconvenience of adding water to dry procaine penicillin is eliminated and ampoules of sterile water are not required. It is stated to be 'reasonably stable' and will keep for twelve months when stored at room temperature. Issued in 10-dose vials. (Glaxo Laboratores Ltd., Greenford, Middlesex.)

PENICILLIN SOLUTION TABLETS A & H are now available in two new strengths: 10,000 and 15,000 units of penicillin per tablet PENICILLIN NONAD TULLE is issued in a new pack containing 40 dressings each 2″ x 2″, a size which should be of interest to general practitioners and casualty officers dealing with minor injuries. (Allen & Hanburys Ltd., Bethnal Green, London, E.2.)

CONTINUED ON PAGE 102

SOROSIL OINTMENT (chloral hydrate, 0.56 per cent. w/w, camphor 0.60 per cent., menthol 1.07 per cent., ether 1.07 per cent., iodine 0.006 per cent., chloroform 1.07 per cent., hyoscyamine 0.00004 per cent. w/w) is a bland non-irritant ointment which is readily absorbed by the skin. Its use is indicated for the amelioration of all types of itching of the skin, such as pruritus, prurigo, eczema, psoriasis, urticaria, chilblains and insect bites, and it is stated to possess definite germicidal and antiseptic properties. Issued in tubes of approximately ½ ounce. (H. R. Napp Ltd., 3 & 4 Clements Inn, London, W.C.2.)

TAORYL tablets (bis[1-(carbo-β-diethylamino-ethoxy)-1-phenyl-cyclopentane]-ethane disulphonate) have been prepared for use in the treatment of irritative coughs, as in acute and chronic disorders of the respiratory tract, laryngitis, tracheitis, pleurisy and hæmoptysis, and smoker's cough. It is also claimed that the relief obtained with Taoryl in bronchial spasm indicates its use in the treatment of asthma, emphysema and whooping-cough. Taoryl is stated to be comparatively non-toxic, and does not cause drowsiness. Issued as sugar-coated tablets of 10 mg., in containers of 20 and 200. (Pharmaceutical Laboratories Geigy Ltd.), National Buildings, Parsonage, Manchester, 3.

SUPPLIES OF AUREOMYCIN

THE Lederle Laboratories Division of Cyanamid Products Ltd., anticipate that supplies of aureomycin will in the near future be available from a new plant at Hirwaun, South Wales. This plant will not only meet domestic demands but will also provide for a considerable volume of exports.

RUTHERFORD MEMORIAL

THE Royal Society has launched an appeal for funds to create a suitable memorial in the shape of scholarships and a Memorial Lecture to the great scientist, Lord Rutherford of Nelson, O.M., F.R.S., father of nuclear physics. In his laboratories many of the world's leaders of physical science were trained, and as Chairman of the Advisory Council of the Department of Scientific and Industrial Research he guided the Government in the encouragement and extension of the use of the scientific method in industry. The Society also proposes to collect and preserve Rutherford's correspondence. Contributions should be sent to the Rutherford Memorial Committee, The Royal Society, Burlington House, London W.1, cheques being drawn to the order of the Society and crossed 'Rutherford Memorial Fund'.

B.M.A. RESEARCH SCHOLARSHIPS

THE Council of the British Medical Association is prepared to receive applications for the following Research Scholarships, tenable for one year and beginning on October 1, 1951: Ernest Hart Memorial Scholarship, £200; Walter Dixon Memorial Scholarship, £200; four Research Scholarships, £150 each—all for research into the causation, prevention, or treatment of disease; Insole Scholarship, £250, for research into the causes and cure of venereal disease. Applications must be made not later than March 31, 1951, on a prescribed form. (Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.)

MEDICAL FILMS

I.C.I. Film Catalogue.—This new film catalogue contains a complete syllabus of all films produced by the Imperial Chemical Industries Co. The subjects cover a wide range—anæsthesia, physiology, the dressing of burns and wounds, pharmacy, industrial dermatitis, penicillin, veterinary and agricultural subjects. Films may be borrowed free of charge. Copies of the catalogue are obtainable on application. (I.C.I. Film Library, Bolton House, Curzon Street, London, W.1.)

Oesophageal Speech after Laryngectomy has been produced by the Department of Health for Scotland in cooperation with the Ear, Nose and Throat Department, Victoria Infirmary, Glasgow. It explains how, after laryngectomy, patients may be trained to produce speech by swallowing air and then regurgitating it while using the moulds of speech in the mouth for articulation. The film is demonstrated by Mr. T. O Howie, Surgeon to the Ear, Nose and Throat Department, Victoria Infirmary. (Central Office of Information, Norgeby House, 83 Baker Street, London, W.1.)

THE Medical Committee of the Scientific Film Association has published *An Interim List of Films of Interest to Pathologists*, some of which have been critically appraised. The Committee requests information on new medical films, especially those made for intramural teaching and research, so that they may be included in the new edition of the 'Catalogue of Medical Films'. (4, Great Russell Street, London, W.C.1. Price 2s. 6d.)

PUBLICATIONS

Annotated Bibliography of Cortisone and A.C.T.H.—The Cortisone Committee of the Empire Rheumatism Council has produced a valuable *Annotated Bibliography of Cortisone, A.C.T.H. and Related Hormonal Substances*, compiled from the English-language publications up to August 1950. It is suggested that in the further instalments, which are to be issued at quarterly intervals, some uniform system of

CONTINUED ON PAGE 104

Intramuscular Heparin

Prolonged heparinisation ensures continuity of flow

The value of anti-coagulant therapy is widely accepted, but in the past the difficulty of maintaining prolonged heparinisation by frequent intravenous injection has limited the use of heparin. Evans have now developed a pyrogen-free solution of heparin in a concentration of 25,000 i.u. per ml. Intramuscular injection of this concentrated solution is followed by gradual absorption of heparin into the blood stream with resultant prolongation of heparinisation. An immediate heparin effect can be achieved by intravenous injection of the concentrated solution. Minimal laboratory investigation is required with heparin therapy and the action of the heparin can be immediately suspended by injection of 5 ml. of 1% protamine sulphate.

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1,000 i.u. per ml.
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Further information on request from Medical Information Department, Speke, Liverpool, 19

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abbreviations for journal titles be used. (The General Secretary, Empire Rheumatism Council, Tavistock House North, Tavistock Square, London, W.C.1., price 5s.)

National Institute for the Blind.—The annual report for 1949-50 emphasizes the present happy relationship between the National Institute for the Blind and the State. 'The Institute, a purely voluntary body, has been fully accepted by the State as a partner in the plans it has laid down and put into force for assisting the blind'. The largest braille publishing house in the Commonwealth, the N.I.B., during the period under review has issued nearly 45,000 books, 27,000 pamphlets, and half a million newspapers and magazines, and has supplied 500 'talking books'. The Sunshine Homes for Blind Babies now number seven, and eleven national homes for the blind are being maintained. Reference is also made to the success of the school of physiotherapy. (224 Great Portland Street, London, W.1.)

Archives of the Middlesex Hospital.—We welcome the reappearance of these *Archives* which were first issued in 1903, and ceased publication in 1916. The first number of the new series, under the editorship of Dr. Douglas McAlpine, is announced for January. (Annual subscription £2 2s. for 4 numbers, single number 12s. 6d. E. & S. Livingstone Ltd., Teviot Place, Edinburgh.)

History Today.—The first number of *History Today*, an illustrated monthly, is to appear this month (January). Edited by Peter Quennell and Alan Hodge, it is written by experts for the general reader and will contain articles on medical history. The magazine has the support of the Historical Association. (2s. 6d. a month, 30s. a year. Historical Association, 21, Bedford Square, London, W.C.1.)

NAPT Annual Report.—The annual report of the National Association for the Prevention of Tuberculosis for 1949-1950, entitled 'A Review of Tuberculosis', is an attractively produced and written booklet, which surveys the Association's various activities in propaganda, education, and social welfare. Two new sections have been added: sanatorium nurses below the rank of matron, and administrators of hospitals, clinics, and dispensaries under the tuberculosis scheme. It is emphasized that the NAPT is a purely voluntary body, receiving no Government grant.

Die Sexualität bei Tuberkulösen.—In this latest addition to the Tuberkulose-Bücherei (Monographien zur Monatsschrift 'Der Tuberkulosearzt'), Dr. H. Westermann of Bonn surveys six hundred tuberculous patients as regards changes in sexuality. His story, illustrated by a number of case histories, is both valuable and interesting, although some of his statements will not readily be accepted in this country. (Stuttgart: Georg Thieme Verlag, 1950. Pp. 30. Price DM. 2.70.).

The Care of Young Babies.—The third edition of this little book by Dr. John Gibbens contains three new chapters—'The Underweight Baby', 'The Overweight Baby', and 'The Sick Baby'. Written especially for mothers and those who have the upbringing of babies, there is much information of interest to practitioners. Some new illustrations have been added. (J. & A. Churchill Ltd., 5s.)

Salt Restriction and the General Practitioner.—The Energen Dietary Service has issued a 4-page leaflet to the medical profession, summarizing present-day knowledge of the rôle of salt in human physiology and of the benefits of 'salt-free' diets or of restriction of salt intake in certain disorders. (Willesden, London, N.W.10.)

Warner's Calendar of Medical History 1951.—This fascinating calendar with illustrated footnotes relating to incidents in medical history is available to members of the medical profession. Notes on infant feeding, peptic ulcer diet, symptoms, signs and treatment of poisoning, infectious diseases, incompatibilities of drugs, the removal of medicinal stains and other items of interest are included. (William R. Warner & Co., Ltd., Power Road, London, W.4.)

OFFICIAL NOTICE

Distribution of Chloramphenicol (Chloromycetin).—Owing to improvement in supplies, Chloramphenicol (Chloromycetin) has been generally available on medical prescription since December 11, 1950, and medical practitioners in the N.H.S. may prescribe it on E.C.10. The Ministry of Health has issued a short memorandum listing the clinical applications of the drug, with special emphasis on those infections in which it is superior to sulphonamides or to penicillin.

INDEX AND BINDING CASES

The index to Vol. **165** (July-December, 1950) will be forwarded to all subscribers with this issue. Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 4s. each, post free. The cases are made to hold six copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 10s. 6d. per volume; this includes the cost of the binding case and return postage.

THE PRACTITIONER: 50 Years Ago. See page 106

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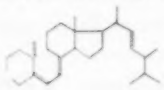

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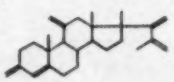
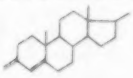


STEROID STRUCTURE

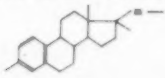
TESTOSTERONE



ANDROGENS

TAB. METHYLTESTOSTERON **B.P.**
Glosso-Sterandryl-5, 10, 25 and 50 mg.
INJ. TESTOSTERON. PROP. **B.P.**
Sterandryl-5, 10, 25, 50, 100 and 500 mg.
IMPLANT of 100 mg. Testosterone Sterandryl-Implant

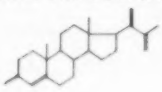
ETHINYL-OESTRADIOL



OESTROGENS

TAB. ETHINYL-OESTRADIOL
Ethin-Oestryl-0.01, 0.05 and 1 mg.
INJ. OESTRADIOL MONOBENZ. **B.P.**
Benzo-Gynoestryl-1 and 5 mg.
IMPLANT of 100 mg. Oestradiol Gynoestryl-Implant

DESOXYCORTICOSTERONE



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THE PRACTITIONER

Fifty Years Ago

'Therefore the moon, the governess of floods,
Pale in her anger, washes all the air,
That rheumatic diseases do abound'.—*A Midsummer Night's Dream, II*, i, 103.

JANUARY, 1901

ENTERING on 'the second century of its existence', '*The Practitioner*', in the words of its Editor (Malcolm Morris), 'may now fairly claim to be one of the "ancient lights" of medical journalism . . . Neither of my venerable contemporaries, the "Lancet" or the "B.M.J.", can say more. Shall we three meet again in a journalistic "respect" . . . at the opening of the twenty-first century, or shall we all be gathered into the great waste paper basket of Time? The question is what superior literary persons call "otiose", both able editors and gentle readers may comfort themselves with the reflection of Goldsmith's cheerful philosopher that 'twill be all the same a hundred years hence'.

The Practitioner's special numbers ('an idea which first found embodiment in this Journal') we are told, 'have met with general approval, and with the imitation which is the sincerest form of flattery, not only on both sides of the Atlantic, but in India'. In the January issue, fifty years ago, the various aspects of rheumatic fever are dealt with by authorities whose names will be remembered in the history of that disease. The first of the 'Original Communications', 'The Epidemiology of Rheumatic Fever', is from the pen of the late Sir Arthur Newsholme, then Medical Officer of Health for Brighton, who regards the condition as 'essentially a soil disease, due to a saprophytic soil organism, which is "drowned out" in wet years, multiplies rapidly in dry years, and is transferred to the human recipient by unknown means. Possibly dust convection accounts for a large proportion of the cases'. In his article, 'The Pathology of Rheumatic Fever', F. J. Poynton, Assistant Physician to the Hospital for Sick Children, Great Ormond Street, reviews the various theories that have been held from time to time, and recalls that in 1900, Alexander Paine and he had isolated in twelve successive cases of rheumatic fever 'a diplococcus which has produced on intravenous inoculation into rabbits the clinical appearances of rheumatic fever'. This organism was found in the blood, urine, and tonsils of the living subject, and in the pericardial exudation and cardiac valves after death. 'This diplococcus which we have isolated is a cause of rheumatic fever. As yet we are not in the position to state that this is the only cause—more extensive researches are requisite—but we believe that this organism will eventually prove to be the actual cause of all cases of rheumatic fever which conform to the usual type of the disease'. To Frederick John Poynton (1869-1943) rheumatism was the dominant interest throughout his professional life, and he resented somewhat bitterly the

Elliott & Fry

Frederick John Poynton, M.D., F.R.C.P.
(1869—1943)

sceptical attitude of his medical colleagues towards his 'discovery'. In 1913 he collected with Alexander Paine, Director of the Cancer Hospital Research Institute in London, in a volume, 'Researches on Rheumatism', 'the chief papers bearing upon a research on the subject of rheumatism which has extended over a period of fifteen years . . . should the essentials of this research be eventually established, we feel that this book will stand as a landmark in the history of rheumatism in this country'.

According to StClair Thomson, Physician to the Throat Hospital, Golden Square, and

FIFTY YEARS AGO—*continued*

Surgeon to the Royal Ear Hospital, writing on 'Rheumatic Fever in Relation to the Throat', 'an undoubted association exists between rheumatism and tonsillitis'. He goes on to say, however, that 'Many of the clinical records are too fragmentary to advance the subject, and it seems to me that the various theories . . . are somewhat premature, and that it is much safer to await further pathological investigation to show which of our clinical deductions are trustworthy'

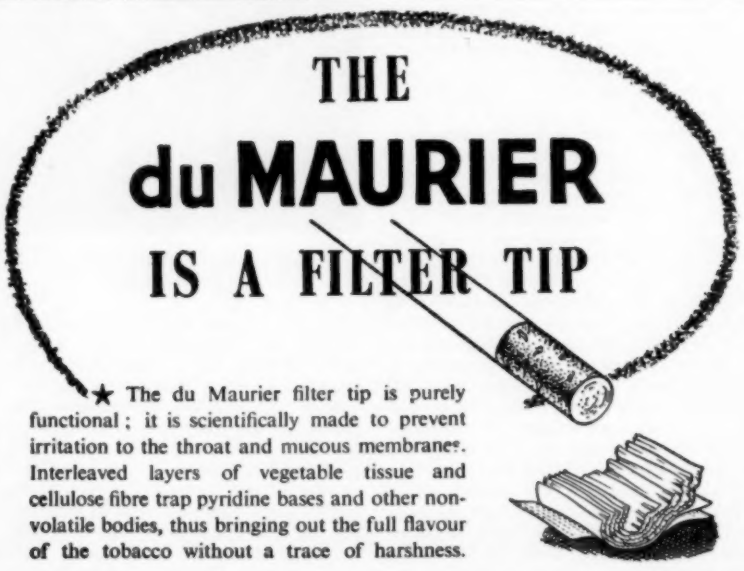
George Alexander Gibson, Physician to the Royal Infirmary, Edinburgh, and one of the foremost authorities in his time on cardiac pathology and therapeutics, contributes a paper on 'The Effects of Rheumatic Fever on the Heart'. It is highly probable, he believes, that 'all cases of acute and sub-acute cardiac diseases are of microbic origin, and all may therefore be termed infective. We have, until recently, had to admit that cases arising in the course of acute rheumatism have not been definitely proved to have their origin in microbic infection, but the admirable work of Poynton and Paine goes a long way to prove such a connection'.

Sir George Frederic Still (1868-1941) fifty years ago was assistant physician for Diseases of Children, King's College Hospital, and Assistant Physician to the Hospital for Sick Children, Great Ormond Street. Then aged thirty-three, he had already made a name for himself in British pædiatrics through his description in 1897 of what is now known as Still's disease. In a characteristically lucid and charming article, 'Rheumatism in Childhood', he writes that 'The rheumatic child is *par excellence* the nervous child. In many cases this is seen in an undue excitability—such children will become almost uncontrollable in their excitement over games and amusements; or, on the other hand, there may be excessive timidity: in some of the older children this is replaced by a sensitivity or shyness which is almost morbid'. Briefly alluding to the association of red hair with rheumatism, he admits that he does not have sufficient statistics to show this.

Arthur P. Luff, Physician in charge of Out-Patients at St. Mary's Hospital, concludes the symposium with 'The Treatment of Rheumatic Fever', and also includes this disease in 'A Review of the Medical Sciences'.

On the day of publication of the New Year's Honours List, let us end with this extract from 'The Month':—'There is something deliciously funny in the proposal that medical men who have distinguished themselves should be "marked in some appropriate way" by the American Medical Association. Is it intended that the man whom it is desired to honour should be tattooed in some appropriate part of his person, and with marks appropriate to the work which has earned him fame?'

W.R.B.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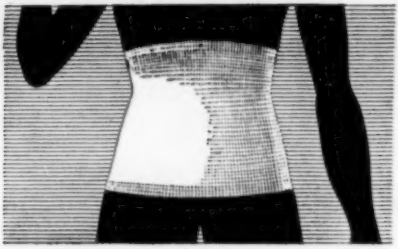

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Medical Superintendent—THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

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For terms and further particulars apply to the Medical Superintendent (Telephone: No. 4354, three lines Northampton), who can be seen in London by appointment.

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Applications are invited from any persons who have been trained in a regular course of Medical or Surgical Study of at least five years' duration in Great Britain or Ireland, and who are legally qualified medical practitioners in Great Britain or Ireland, who are natural born British subjects of European descent, for short-service commissions of four years in the Royal Australian Army Medical Corps. Rank—Captain. Age 23 to 35. Medical Classification—completely fit for all duties in any locality.

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